CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-103

***Name*:** Ipratropium Bromide Nasal Solution, 0.06%, (Nasal Spray), 0.042 mg/spray

***Sponsor*:** Bausch & Lomb Pharmaceuticals, Inc.

***Approval Date*:** March 31, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-103

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APPLICATION NUMBER:

ANDA 76-103

APPROVAL LETTER

ANDA 76-103

MAR 31 2003

Bausch & Lomb Pharmaceuticals, Inc.
Attention: Joseph B. Hawkins
8500 Hidden River Parkway
Tampa, FL 33637

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated January 17, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Ipratropium Bromide Nasal Solution, 0.06%, (Nasal Spray), 0.042 mg/spray, packaged in a 15 mL bottle fitted with a metered nasal spray pump.

Reference is also made to your amendments dated September 26, 2001, and September 19, and October 3, 2002. We also acknowledge your correspondence dated March 25, 2003 addressing the I-327 exclusivity listed in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the Orange Book.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Ipratropium Bromide Nasal Solution, 0.06%, (Nasal Spray) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Atrovent® Nasal Spray, 0.06%, of Boehringer Ingelheim Pharmaceuticals, Inc.).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies that may be identified.

Sincerely yours,

Gary Buehler 3/31/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-103
Division File
Field Copy
HFD-610/R. West
HFD-610/Orange Book
HFD-330
HFD-205

Endorsements:
HFD-625/M.Shaikh/ Mujahid Shaikh 2/10/03
HFD-625/M.Smela/ M Smela* 2/11/03
HFD-617/P.Chen/ Peter Chen 2/10/03
HFD-613/A.Payne/ Anne 2/10/03
HFD-613/J.Grace/ Jgrace 2/10/2003

Robert Lyndon 3/25/2003

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F/T by

APPROVAL

* Bioequivalence acceptable on 1/23/03. Reconsidered and found unacceptable on 3/11/03. Reconsidered and found acceptable on 3/14/03. No new amendments. M Smela 3/17/03

Released 3/18/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-103

LABELING

MAR 3 1 2003

Rx only
FOR INTRANASAL USE ONLY
Usual Dosage:
Read full package insert and patient instructions.
KEEP OUT OF REACH OF CHILDREN.
Storage: Store between 15°–30°C (59°–86°F).
Keep tightly closed.
Avoid freezing.
AB39911 XG57849 REV: 7/01-01
FDA DRAFT 2

NDC 24208-399-15

Ipratropium Bromide

Nasal Solution

0.06% (Nasal Spray)

15 mL (165 metered sprays)
42 mcg/spray

OTHER INGREDIENTS:
Benzalkonium chloride, edetate disodium, sodium chloride, purified water.

WARNING: Avoid spraying ipratropium bromide nasal spray in or around the eyes.

Pharmaceuticals, Inc.
Tampa, FL 33637

3 3/8" x 13/16" 1" Non UV at left 1/16" Margins
CORE 39911
Art is at 100%
3 Color: Black, Process Blue, PMS 293
L-1601
PHARMACODE#

ENLARGED TO 150%
BY FOIA STAFF

APP 3/31/03 76-103

CORE 39911
15 mL CARTON
Box Dimensions: 1 7/8" x 1 5/8" x 4"
3 Color: Black, Process Blue, PMS 293
L-2069
PHARMACODE#
SCANNER BAR LOCATION:

Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray)

BAUSCH & LOMB

NDC 24208-399-15

Ipratropium Bromide
Nasal Solution
0.06%
(Nasal Spray)

Rx only

15 mL (165 metered sprays)
42 mcg/spray

CONTAINS:
Ipratropium bromide 0.06% in a pH-adjusted to 4.7, isotonic aqueous solution which also contains benzalkonium chloride, edetate disodium, sodium chloride.

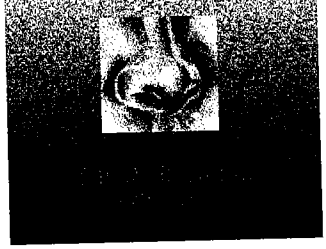
USUAL DOSAGE:
Two sprays per nostril, three or four times daily. Read accompanying full package insert and patient instructions.

WARNING:
Avoid spraying ipratropium bromide nasal spray in or around the eyes.

BAUSCH & LOMB

NDC 24208-399-15

Ipratropium Bromide
Nasal Solution
0.06%
(Nasal Spray)



Rx only

15 mL (165 metered sprays)
42 mcg/spray

KEEP OUT OF REACH OF CHILDREN.

Storage:
Store between 15°– 30°C (59°– 86°F).
Keep tightly closed.
Avoid freezing.

APPROVED
MAR 31 2003

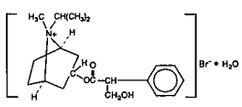
Bausch & Lomb
Pharmaceuticals, Inc.
Tampa, FL 33637

XQ91905
REV. 7/01-01
AB39911
FDA DRAFT.2

ATTENTION PHARMACIST: Detach "Patient's Instructions for Use" from package insert and dispense with product.

Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray)

APPROVED
MAR 31 2003



ipratropium bromide monohydrate $(C_{20}H_{30}BrNO_3 \cdot H_2O)$ Mol. Wt. 430.4

DESCRIPTION: The active ingredient in Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) is ipratropium bromide monohydrate. It is an anticholinergic agent chemically described as 8-azoniabicyclo (3.2.1) octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate (*endo,syn*)-, (±)-: a synthetic quaternary ammonium compound, chemically related to atropine. Its structural formula is:

Ipratropium bromide is a white to off-white, crystalline substance. It is freely soluble in lower alcohols and water, existing in an ionized state in aqueous solutions, and relatively insoluble in non-polar media.

Ipratropium bromide nasal solution 0.06% (Nasal Spray) is a metered-dose, manual pump spray unit which delivers 42 mcg ipratropium bromide (on an anhydrous basis) per spray (70 µL) in an isotonic, aqueous solution with pH-adjusted to 4.7. It also contains benzalkonium chloride, edetate disodium, sodium chloride, sodium hydroxide, hydrochloric acid, and purified water. Each bottle contains 165 sprays.

CLINICAL PHARMACOLOGY: Mechanism of Action: Ipratropium bromide is an anticholinergic agent that inhibits vagally-mediated reflexes by antagonizing the action of acetylcholine at the cholinergic receptor. In humans, ipratropium bromide has anti-secretory properties and, when applied locally, inhibits secretions from the serous and seromucous glands lining the nasal mucosa. Ipratropium bromide is a quaternary amine that minimally crosses the nasal and gastrointestinal membrane and the blood-brain barrier, resulting in a reduction of the systemic anticholinergic effects (e.g., neurologic, ophthalmic, cardiovascular, and gastrointestinal effects) that are seen with tertiary anticholinergic amines.

Pharmacokinetics: Absorption: Ipratropium bromide is poorly absorbed into the systemic circulation following oral administration (2-3%). Less than 20% of an 84 mcg per nostril dose was absorbed from the nasal mucosa of normal volunteers, induced-cold adult volunteers, naturally-acquired common cold pediatric patients, or perennial rhinitis adult patients.

Distribution: Ipratropium bromide is minimally bound (0 to 9% *in vitro*) to plasma albumin and a_1-acid glycoprotein. Its blood/plasma concentration ratio was estimated to be about 0.89. Studies in rats have shown that ipratropium bromide does not penetrate the blood-brain barrier.

Metabolism: Ipratropim bromide is partially metabolized to ester hydrolysis products, tropic acid, and tropane. These metabolites appear to be inactive based on *in vitro* receptor affinity studies using rat brain tissue homogenates.

Elimination: After intravenous administration of 2 mg ipratropium bromide to 10 healthy volunteers, the terminal half-life of ipratropium bromide was approximately 1.6 hours. The total body clearance and renal clearance were estimated to be 2,505 and 1,019 ml/min respectively. The amount of the total dose excreted unchanged in the urine (Ae) within 24 hours was approximately one-half of the administered dose.

Pediatrics: Following administration of 84 mcg of ipratropium bromide per nostril three times a day in patients 5-18 years old (n=42) with naturally-acquired common cold, the mean amount of the total dose excreted unchanged in the urine of 7.8% was comparable to 84 mcg per nostril four times a day in an adult induced common cold population (n=22) of 7.3 to 8.1%. Plasma ipratropium concentrations were relatively low (ranging from undetectable up to 0.62 ng/mL). No correlation of the amount of the total dose excreted unchanged in the urine (Ae) with age or gender was observed in the pediatric population.

Special Populations: Gender does not appear to influence the absorption or excretion of nasally administered ipratropium bromide. The pharmacokinetics of ipratropium bromide have not been studied in patients with hepatic or renal insufficiency or in the elderly.

Drug-Drug Interactions: No specific pharmacokinetic studies were conducted to evaluate potential drug-drug interactions.

Pharmacodynamics: In two single dose trials (n=17), doses up to 336 mcg of ipratropium bromide did not significantly affect pupillary diameter, heart rate or systolic/diastolic blood pressure. Similarly, ipratropium bromide nasal solution 0.06% (Nasal Spray) in adult patients (n=22) with induced-colds, (84 mcg/nostril four times a day) and in pediatric patients (n=45) with naturally acquired common colds (84 mcg/nostril three times a day) had no significant effects on pupillary diameter, heart rate, or systolic/diastolic blood pressure.

Controlled clinical trials demonstrated that intranasal fluorocarbon-propelled ipratropium bromide does not alter physiologic nasal functions (e.g., sense of smell, ciliary beat frequency, mucociliary clearance, or the air conditioning capacity of the nose).

Clinical Trials: The clinical trials for ipratropium bromide nasal solution 0.06% (Nasal Spray) were conducted in patients with rhinorrhea associated with naturally occurring common colds. In two controlled four day comparisons of ipratropium bromide nasal solution 0.06% (Nasal Spray) (84 mcg per nostril, administered three or four times daily; n=352) with its vehicle (n=351), there was a statistically significant reduction of rhinorrhea, as measured by both nasal discharge weight and the patients' subjective assessment of severity of rhinorrhea using a visual analog scale. These significant differences were evident within one hour following dosing. There was no effect of ipratropium bromide nasal solution 0.06% (Nasal Spray) on degree of nasal congestion or sneezing. The response to ipratropium bromide nasal solution 0.06% (Nasal Spray) did not appear to be affected by age or gender. No controlled clinical trials directly compared the efficacy of three times daily versus four times daily treatment.

INDICATIONS AND USAGE: Ipratropium bromide nasal solution 0.06% (Nasal Spray) is indicated for the symptomatic relief of rhinorrhea associated with the common cold for adults and children age 5 years and older. Ipratropium bromide nasal solution 0.06% (Nasal Spray) does not relieve nasal congestion or sneezing associated with the common cold.

The safety and effectiveness of the use of ipratropium bromide nasal solution 0.06% (Nasal Spray) beyond four days in patients with the common cold has not been established.

CONTRAINDICATIONS: Ipratropium bromide nasal solution 0.06% (Nasal Spray) is contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, or to any of the other ingredients.

WARNINGS: Immediate hypersensitivity reactions may occur after administration of ipratropium bromide, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm and oropharyngeal edema.

PRECAUTIONS: General: Ipratropium bromide nasal solution 0.06% (Nasal Spray) should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction, particularly if they are receiving an anticholinergic by another route. Cases of precipitation or worsening of narrow-angle glaucoma and acute eye pain have been reported with direct eye contact of ipratropium bromide administered by oral inhalation.

Information for Patients: Patients should be advised that temporary blurring of vision, precipitation or worsening of narrow-angle glaucoma or eye pain may result if ipratropium bromide nasal solution 0.06% (Nasal Spray) comes into direct contact with the eyes. Patients should be instructed to avoid spraying ipratropium bromide nasal solution 0.06% (Nasal Spray) in or around their eyes. Patients who experience eye pain, blurred vision, excessive nasal dryness or episodes of nasal bleeding should be instructed to contact their doctor. Patients should be reminded to carefully read and follow the accompanying Patient's Instructions for Use.

Drug Interactions: No controlled clinical trials were conducted to investigate drug-drug interactions. Ipratropium bromide nasal solution 0.06% (Nasal Spray) is minimally absorbed into the systemic circulation; nonetheless, there is some potential for an additive interaction with other concomitantly administered anticholinergic medications, including ipratropium bromide for oral inhalation.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In two-year oral carcinogenicity studies in rats and mice, ipratropium bromide at oral doses up to 6 mg/kg (approximately 70 and 35 times the maximum recommended daily intranasal dose in adults, respectively, and approximately 45 and 25 times the maximum recommended daily intranasal dose in children, respectively, on a mg/m² basis) showed no carcinogenic activity. Results of various mutagenicity studies (Ames test, mouse dominant lethal test, mouse micronucleus test, and chromosome aberration of bone marrow in Chinese hamsters) were negative. Fertility of male or female rats was unaffected by ipratropium bromide at oral doses up to 50 mg/kg (approximately 600 times the maximum recommended daily intranasal dose in adults on a mg/m² basis). At an oral dose of 500 mg/kg (approximately 16,000 times the maximum recommended daily intranasal dose in adults on a mg/m² basis), ipratropium bromide produced a decrease in the conception rate.

Pregnancy: *TERATOGENIC EFFECTS Pregnancy Category B.* Oral reproduction studies were performed at doses of 10 mg/kg in mice, 1,000 mg/kg in rats and 125 mg/kg in rabbits. These doses correspond, in each species respectively, to approximately 60, 12,000, and 3,000 times the maximum recommended daily intranasal dose in adults on a mg/m² basis. Inhalation reproduction studies were conducted in rats and rabbits at doses of 1.5 and 1.8 mg/kg, respectively (approximately 20 and 45 times, respectively, the maximum recommended daily intranasal dose in adults on a mg/m² basis). These studies demonstrated

PHARMACIST — DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT'S INSTRUCTIONS FOR USE:

Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray)

APPROVED
MAR 31 2003

Ipratropium bromide nasal solution 0.06% (Nasal Spray) is indicated for the symptomatic relief of rhinorrhea (runny nose) associated with the common cold for adults and children age 5 years and older. Ipratropium bromide nasal solution 0.06% (Nasal Spray) does not relieve nasal congestion or sneezing associated with the common cold. Do not use ipratropium bromide nasal solution 0.06% (Nasal Spray) for longer than four days unless instructed by your physician. Read complete instructions carefully and use only as directed.

To Use:

1. Remove the clear plastic dust cap and the safety clip from the nasal spray pump (Figure 1). The safety clip prevents the accidental discharge of the spray in your pocket or purse.

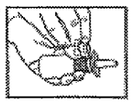


Figure 1

2. The nasal spray pump must be primed before ipratropium bromide nasal solution 0.06% (Nasal Spray) is used for the first time. To prime the pump, hold the bottle with your thumb at the base and your index and middle fingers on the white shoulder area. Make sure the bottle points upright and away from your eyes. Press your thumb firmly and quickly against the bottle seven times (Figure 2). The pump is now primed and can be used. Your pump should not have to be reprimed unless you have not used the medication for more than 24 hours; reprimming the pump will only require two sprays. If you have not used your nasal spray for more than seven days, reprimming the pump will require seven sprays.

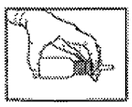


Figure 2

3. Before using ipratropium bromide nasal solution 0.06% (Nasal Spray), blow your nose gently to clear your nostrils if necessary.

4. Close one nostril by gently placing your finger against the side of your nose, tilt your head slightly forward and, keeping the bottle upright, insert the nasal tip into the other nostril (Figure 3). Point the tip toward the back and outer side of the nose.

Figure 3

5. Press firmly and quickly upwards with the thumb at the base while holding the white shoulder portion of the pump between your index and middle fingers. Following each spray sniff deeply and breathe out through your mouth.

6. After spraying the nostril and removing the unit, tilt your head backwards for a few seconds to let the spray spread over the back of the nose.

7. Repeat steps 4 through 6 in the same nostril.

8. Repeat steps 4 through 7 in the other nostril (i.e., two sprays per nostril).

no evidence of teratogenic effects as a result of ipratropium bromide. At oral doses above 90 mg/kg in rats (approximately 1,100 times the maximum recommended daily intranasal dose in adults on a mg/m² basis) embryotoxicity was observed as increased resorption. This effect is not considered relevant to human use due to the large doses at which it was observed and the difference in route of administration. However, no adequate or well controlled studies have been conducted in pregnant women. Because animal reproduction studies are not always predictive of human response, ipratropium bromide should be used during pregnancy only if clearly needed.

Nursing Mothers: It is known that some ipratropium bromide is systemically absorbed following nasal administration; however the portion which may be excreted in human milk is unknown. Although lipid-insoluble quaternary bases pass into breast milk, the minimal systemic absorption makes it unlikely that ipratropium bromide would reach the infant in an amount sufficient to cause a clinical effect. However, because many drugs are excreted in human milk, caution should be exercised when ipratropium bromide nasal solution 0.06% (Nasal Spray) is administered to a nursing woman.

Pediatric Use: The safety of ipratropium bromide nasal solution 0.06% (Nasal Spray) at a dose of two sprays (84 mcg) per nostril three times a day (total dose 504 mcg/day) for two to four days has been demonstrated in two clinical trials involving 362 pediatric patients 5-11 years of age with naturally acquired common colds. In this pediatric population ipratropium bromide nasal solution 0.06% (Nasal Spray) had an adverse event profile similar to that observed in adolescent and adult patients. When ipratropium bromide was concomitantly administered with an oral decongestant (pseudoephedrine HCl) in 122 children ages 5-12 years, and concomitantly administered with an oral decongestant/antihistamine combination (pseudoephedrine HCl/chlorpheniramine maleate) in 123 children ages 5-12 years, adverse event profiles were similar to ipratropium bromide alone. The effectiveness of ipratropium bromide nasal solution 0.06% (Nasal Spray) for the treatment of rhinorrhea associated with the common cold in this pediatric age group is based on extrapolation of the demonstrated efficacy of ipratropium bromide nasal solution 0.06% (Nasal Spray) in adolescents and adults with this condition and the likelihood that the disease course, pathophysiology, and the drug's effects are substantially similar to that of adults. The recommended dose for the pediatric population is based on cross-study comparisons of the efficacy of ipratropium bromide nasal solution 0.06% (Nasal Spray) in adults and pediatric patients and on its safety profile in both adults and pediatric patients. The safety and effectiveness of ipratropium bromide nasal solution 0.06% (Nasal Spray) in pediatric patients under 5 years of age have not been established.

ADVERSE REACTIONS: Adverse reaction information on ipratropium bromide nasal solution 0.06% (Nasal Spray) in patients with the common cold was derived from two multicenter, vehicle-controlled clinical trials involving 1,276 patients (195 patients on ipratropium bromide nasal solution 0.03% (Nasal Spray), and 352 patients on ipratropium bromide nasal solution 0.06% (Nasal Spray), 189 on ipratropium bromide nasal solution 0.12% (Nasal Spray), 351 patients on vehicle and 189 patients receiving no treatment).

The following table shows adverse events reported for patients who received ipratropium bromide nasal solution 0.06% (Nasal Spray) at the recommended dose of 84 mcg per nostril, or vehicle, administered three or four times daily, where the incidence is 1% or greater in the ipratropium bromide group and higher in the ipratropium bromide group than in the vehicle group.

Percent of Patients Reporting Events[1]

	Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) (n=352)	Vehicle Control (n=351)
Epistaxis[2]	8.2%	2.3%
Dry Mouth/Throat	1.4%	0.3%
Nasal Congestion	1.1%	0.0%
Nasal Dryness	4.8%	2.8%

[1]This table includes adverse events for which the incidence was 1% or greater in the ipratropium bromide group and higher in the ipratropium bromide group than in the vehicle group.

[2] Epistaxis reported by 5.4% of ipratropium bromide patients and 1.4% of vehicle patients, blood-tinged mucus by 2.8% of ipratropium bromide patients and 0.9% of vehicle patients.

Ipratropium bromide nasal solution 0.06% (Nasal Spray) was well tolerated by most patients. The most frequently reported adverse events were transient episodes of nasal dryness or epistaxis. The majority of these adverse events (96%) were mild or moderate in nature, none was considered serious, and none resulted in hospitalization. No patient required treatment for nasal dryness, and only three patients (<1%) required treatment for epistaxis, which consisted of local application of pressure or a moisturizing agent (e.g., petroleum jelly). No patient receiving ipratropium bromide nasal solution 0.06% (Nasal Spray) was discontinued from the trial due to either nasal dryness or bleeding.

Adverse events reported by less than 1% of the patients receiving ipratropium bromide nasal solution 0.06% (Nasal Spray) during the controlled clinical trials which are potentially related to ipratropium bromide's local effects or systemic anticholinergic effects include: taste perversion, nasal burning, conjunctivitis, coughing, dizziness, hoarseness, palpitation, pharyngitis, tachycardia, thirst, tinnitus and blurred vision. Additional anticholinergic effects noted with other ipratropium bromide dosage forms (ipratropium bromide inhalation solution, ipratropium bromide inhalation aerosol, and ipratropium bromide nasal spray 0.03% [Nasal Spray]) include: precipitation or worsening of narrow-angle glaucoma, urinary retention, prostate disorders, constipation, and bowel obstruction.

There no reports of allergic-type reactions in the controlled clinical trials. Allergic-type reactions such as skin rash, angioedema of the tongue, lips and face, urticaria, laryngospasm and anaphylactic reactions have been reported with other ipratropium bromide products. No controlled trial was conducted to address the relative incidence of adverse events for three times daily versus four times daily therapy.

OVERDOSAGE: Acute overdosage by intranasal administration is unlikely since ipratropium bromide is not well absorbed systemically after intranasal or oral administration. Following administration of a 20 mg oral dose (equivalent to ingesting more than two bottles of ipratropium bromide nasal solution 0.06% [Nasal Spray]) to 10 male volunteers, no change in heart rate or blood pressure was noted. Following a 2 mg intravenous infusion over 15 minutes to the same 10 male volunteers, plasma ipratropium concentrations of 22-45 ng/mL were observed (>100 times the concentrations observed following intranasal administration). Following intravenous infusion these 10 volunteers had a mean increase of heart rate of 50 bpm and less than 20 mm Hg change in systolic or diastolic blood pressure at the time of peak ipratropium levels.

Oral median lethal doses of ipratropium bromide were greater than: 1,000 mg/kg in mice (approximately 6,000 and 3,800 times the maximum recommended daily intranasal dose in adults and children, respectively, on a mg/m² basis) 1,700 mg/kg in rats (approximately 21,000 and 13,000 times the maximum recommended daily intranasal dose in adults and children, respectively, on a mg/m² basis) and 400 mg/kg in dogs (approximately 16,000 and 10,000 times the maximum recommended daily intranasal dose in adults and children, respectively, on a mg/m² basis).

DOSAGE AND ADMINISTRATION: The recommended dose of ipratropium bromide nasal solution 0.06% (Nasal Spray) is two sprays (84 mcg) per nostril three or four times daily (total dose 504 to 672 mcg/day) for symptomatic relief of rhinorrhea associated with the common cold in adults and children age 5 years and older. Optimum dosage varies with the response of the individual patient. The recommended dose of ipratropium bromide nasal solution 0.06% (Nasal Spray) for children age 5-11 years is two sprays (84 mcg) per nostril three times daily (total dose 504 mcg/day). The safety and effectiveness of the use of ipratropium bromide nasal solution 0.06% (Nasal Spray) beyond four days in patients with the common cold have not been established.

Initial pump priming requires seven sprays of the pump. If used regularly as recommended, no further priming is required. If not used for more than 24 hours, the pump will require two sprays, or if not used for more than seven days, the pump will require seven sprays to reprime.

HOW SUPPLIED: Ipratropium bromide nasal solution 0.06% (Nasal Spray) is supplied in a white high density polyethylene (HDPE) bottle fitted with a metered nasal spray pump, a safety clip to prevent accidental discharge of the spray, and a clear plastic dust cap. It contains 16.6 g of product formulation, 165 sprays, each delivering 42 mcg of ipratropium bromide per spray (70 µL), or 10 days of therapy at the maximum recommended dose (two sprays per nostril four times a day).

STORAGE: Store between 15°-30°C (59°-86°F). Keep tightly closed. Avoid freezing. Keep out of reach of children. Avoid spraying in or around the eyes.

Patients should be reminded to read and follow the accompanying Patient's Instructions for Use, which should be dispensed with the product.

Rx only

Bausch & Lomb
Pharmaceuticals, Inc.
Tampa, FL 33637

AB39911
XO51015 **(Folded)** REV. 7/01-01
FDA DRAFT.2

PHARMACIST — DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

CAUTION:

Ipratropium bromide nasal solution 0.06% (Nasal Spray) is intended to relieve your rhinorrhea (runny nose) with regular use. It is therefore important that you use ipratropium bromide nasal solution 0.06% (Nasal Spray) as prescribed by your physician. For most patients, some improvement in runny nose is usually apparent following the first dose of treatment with ipratropium bromide nasal solution 0.06% (Nasal Spray). Do not use ipratropium bromide nasal solution 0.06% (Nasal Spray) for longer than four days unless instructed by your physician.

Do not spray ipratropium bromide nasal solution 0.06% (Nasal Spray) in your eyes. Should this occur, immediately flush your eye with cool tap water for several minutes. If you accidentally spray ipratropium bromide nasal solution 0.06% (Nasal Spray) in your eyes, you may experience a temporary blurring of vision and increased sensitivity to light, which may last a few hours. Should eye pain or blurred vision occur, contact your doctor.

Should you experience excessive nasal dryness or episodes of nasal bleeding contact your doctor.

You should not use this drug if you have glaucoma or difficult urination due to an enlargement of the prostate, unless directed by a physician.

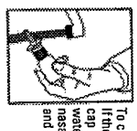
Ipratropium bromide nasal solution 0.06% (Nasal Spray) should not be used during pregnancy or breastfeeding, unless directed by a physician. It is not known whether ipratropium bromide is excreted in human milk; however, many drugs are excreted in human milk.

STORAGE: Store between 15°-30°C (59°-86°F). Keep tightly closed. Avoid freezing. Keep out of reach of children.

Rx only

Bausch & Lomb
Pharmaceuticals, Inc.
Tampa, FL 33637
©Bausch & Lomb Pharmaceuticals, Inc.
AB39911 XO51015 **(Folded)** REV. 7/01-01

Figure 4



To clean:
If the nasal tip becomes clogged, remove the clear plastic dust cap and safety clip. Hold the nasal tip under running, warm tap water (Figure 4) for about a minute. Dry the nasal tip, reprime the nasal spray pump (step 2 above), and replace the plastic dust cap end safety clip.

9. Replace the clear plastic dust cap and safety clip.

10. You should not take extra doses or stop using ipratropium bromide nasal solution 0.06% (Nasal Spray) without consulting your physician.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-103

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **76-103** Date of Submission: Jan. 17. 01
Applicant's Name: Bausch & Lomb
Established Name: **Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) - 0.042 mg/spray)**

Labeling Deficiencies:

1. CONTAINER 42 mcg/spray (165 sprays) - Revise the product name to read: Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) rather than Ipratropium Bromide Nasal Spray 0.06%
2. CARTON – 42 mcg/spray (1 x165 sprays) – See revised name change
3. INSERT – See revised name change.
4. PATIENT LEAFLET – See revised name change.

Please revise your labels and labeling, as instructed above, and submit 12 final print labels and labeling or draft if you prefer.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Patent Data For NDA – 20-394: no unexpired patents. Paragraph II filed.

Exclusivity Data/

supplement No	Expiration	Use Code	Description	How Filed	Labeling Impact
s-001/app. Nov. 9. 98	Nov 09, 01	I-243	Use in the symptomatic relief of rhinorrhea associated with the common cold in children age 5 to 11 years		Has in insert
s-004/app 10/27/00	*	*	Use in the symptomatic relief of rhinorrhea associated with seasonal allergic rhinitis in patients 5 years of age and older		No impact

***consulted Ms Holovac on whether they will get exclusivity she said they will but it will take a couple of weeks. Firms will need to update exclusivity statement once it is available publicly.**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:

Container Labels:

Carton Labeling:

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No.

What is the RLD on the 356(h) form: atrovent

NDA Number: 20-394

NDA Drug Name: Ipratropium bromide Nasal spray 0.06%

NDA Firm: Boehringer Ingel

Date of Approval of NDA Insert and supplement #: s-001 approved in FPL Jan. 22, 99.

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Labels submitted with application

Basis of Approval for the Carton Labeling: Labels submitted with application

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N/A
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	

Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			X
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?			X
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			X
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

NOTES/QUESTIONS TO THE CHEMIST: The orange book list this product as a Nasal metered spray. However our acceptance letter calls it a solution. If think the acceptance letter for filling is incorrect. Do you concur??

FOR THE RECORD:

1. Review based on the labeling of Atrovent (Boehring Ingelhemin, NDA 20-394/S-001, revised 11/98; approved nov.l 1, 98 draft and Jan 22, 99 FPL).
2. Storage Conditions:
   NDA - Store tightly closed betwe 15-30C. Avoid Freezing, keep out of reach of children
   ANDA - same
   USP – not applicable
3. Dispensing Recommendations:

NDA – Dispense with Patient instruction sheet.
ANDA - same
USP –

4. Product Line:
The innovator markets their product in in a white HDPE bottle fitted with a white and clear metered nasal spray pump, a green safety clip and a clear plastic dust cap. It contains 16.6g of product, 165 sprays, at 42 mcg/spray or 10 days of therapy at the maxium dose of 2 sprays per nostril 4 x daily.
The applicant proposes to market their product in same as RLD except color of saftey clip.

5. Inactive Ingredients:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 271 (red Volume 1.1).

Date of Review: May 15, 2001 **Date of Submission: Jan. 17, 2001**

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cc: ANDA: 76-103
DUP/DIVISION FILE
HFD-613/APayne/ JGrace (no cc)
V:firmsam/bausch/let&rev/76103na1.l
Review

John D'Grace 5/31/2001
JGrace 5/23/01

APPEARS THIS WAY
ON ORIGINAL

3.1

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	**76-103**
Date of Submission	April 11, 2002
Applicant	Bausch & Lomb
Drug Name	Ipratropium Bromide Nasal Solution
Strength(s)	0.06% (Nasal Spray) 0.042 mg/spray

FPL Approval Summary		
Container Labels		**Submitted**
0.06%	15 mL	Apr. 11, 2002 vol. 3.1
Carton Labeling		
0.6%	1 x 15 mL	Apr. 11, 2002 vol. 3.1
Package Insert Labeling	#X051015Rev. 7/01-01	Apr. 11, 2002 vol. 3.1
Patient Leaflet	#X051015Rev. 7/01-01	Apr. 11, 2002 vol. 3.1

BASIS OF APPROVAL:

Patent Data For NDA 20-394: NO UNEXPIRED PATENTS

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None				

Exclusivity Data For NDA 20-394:

Code/sup	Expiration	Description	Labeling impact
S-001/app. Nov. 9. 98	Nov 09, 01	Use in the symptomatic relief of rhinorrhea associated with the common cold in children age 5 to 11 years	Same As
S-004/app 10/27/00 T-327	Oct. 27, 2003	Use in the symptomatic relief of rhinorrhea associated with seasonal allergic rhinitis in patients 5 years of age and older	Carve out

Reference Listed Drug	
RLD on the 356(h) form	ATROVENT® Nasal Spray
NDA Number	20-394
RLD established name	Ipratropium Bromide Nasal Solution, 0.06%
Firm	Boehringer Ingelheim
Currently approved PI	S-001
AP Date	Nov. 09, 1998

Note.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			X
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X

Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?			X
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			X
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. Review based on the labeling of Atrovent (Boehring Ingelhemin, NDA 20-394/S-001, revised 11/98; approved nov.l 1, 98 draft and Jan 22, 99 FPL).
2. Storage Conditions:
   NDA - Store tightly closed betwe 15-30C. Avoid Freezing, keep out of reach of children
   ANDA - same
   USP – not applicable
3. Dispensing Recommendations:
   NDA – Dispense with Patient instruction sheet.
   ANDA - same
   USP –
4. Product Line:
   The innovator markets their product in in a white HDPE bottle fitted with a white and clear metered nasal spray pump, a green safety clip and a clear plastic dust cap. It contains 16.6g of product, 165 sprays, at 42 mcg/spray or 10 days of therapy at the maxium dose of 2 sprays per nostril 4 x daily.
   The applicant proposes to market their product in same as RLD except color of saftey clip.
5. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 271 (red Volume 1.1) .

Date of Review: May 21, 2002 **Date of Submission: April 11, 2002**

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cc: ANDA: 76-103
DUP/DIVISION FILE
HFD-613/APayne/ JGrace (no cc)
V:firmsam/bausch/let&rev/76103AP.Lab Review

5/21/02

5/28/02

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-103

CHEMISTRY REVIEWS

1. CHEMISTRY REVIEW NO. 1

2. ANDA # *76-103*

3. NAME AND ADDRESS OF APPLICANT

Bausch & Lomb Pharmaceuticals, Inc.
Attention: Joseph B. Hawkins
8500 Hidden River Parkway
Tampa, FL 33637

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Ipratropium Bromide

13. DOSAGE FORM
Nasal Spray

14. STRENGTH(s)
0.06%

10. PHARMACOLOGICAL CATEGORY
Anticholinergic agent for perennial rhinitis

11. Rx or OTC Rx

4. LEGAL BASIS FOR SUBMISSION
NDA *20394*, Atrovent®, Boehringer Ingelheim

5. SUPPLEMENT(s)
N/A

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Vol. A1.1 to 1.16: (A1.4 to A1.16 are Bio only.)

01/17/01 Original ANDA
02/14/01 Acknowledgement - acceptable for filing 01/18/01
05/07/01 NC - Alternate Test Lab

Vol. A2.1:

02/14/01 NC - Electronic Bio files

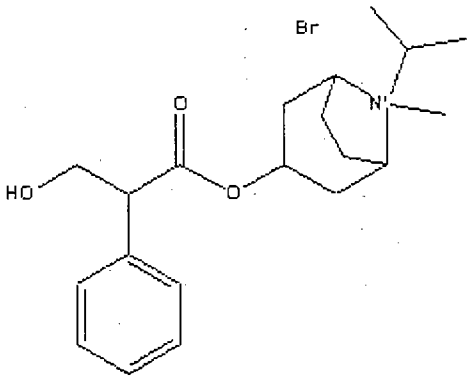
12. RELATED IND/NDA/DMF(s) See DMF Checklist.

I finished reviewing B&L's ANDA 76-025 for the 0.03% strength on 4/26/01. Italicized information in this review for 76-103 is different from the information for 76-025.

15. CHEMICAL NAME AND STRUCTURE

Ipratropium bromide monohydrate [66985-17-9]
CAS number for anhydrous form is 22254-24-6.

$C_{20}H_{30}BrNO_3-H_2O$
412.3659 anhydrous, 430.38 monohydrate



16. RECORDS AND REPORTS N/A

17. COMMENTS

There are **deficiencies** in the following Review Points: 23.A, 23.B, 25, 26, *28.A*, 28.B, 29

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)
A nasal spray is not required to be sterile.

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS
We will schedule the study after the test method issues are resolved.

32. LABELING
The labeling information is ***deficient***.

33. ESTABLISHMENT INSPECTION
The facilities were found **acceptable** 3/14/01.

34. BIOEQUIVALENCE STATUS
Deficiencies were faxed to B&L on 5/30/01.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 76-103 is **NOT APPROVED - MAJOR AMENDMENT requested.**

19. REVIEWER: DATE COMPLETED:

Eugene L. Schaefer, Ph.D. 6/27/01

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

prior to its completion. Additionally, please provide all current methods for drug substance acceptance and drug product release in a separate section of your amendment to facilitate the process.

3. Labeling deficiencies will also need to be addressed in your reply.

4. An acceptable compliance evaluation is necessary for approval. We have requested an evaluation from the Office of Compliance.

Sincerely yours,

Paul S. Lee for 7/5/01

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-103
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates): ES 7/2/01

HFD-625/ELSchaefer, Chemist/6/27/01

HFD-625/MSmela, Team Leader/6/28/01 MSmela 7/2/01

HFD-617/MDillahunt, Project Manager/6/29/01 MDillahunt 7/2/01

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F/T by: DJ 7/2/01

CHEMISTRY REVIEW - NOT APPROVABLE - MAJOR

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. **2**

2. ANDA # **76-103**

3. NAME AND ADDRESS OF APPLICANT
Bausch & Lomb Pharmaceuticals, Inc.(B&L)
Attention: Joseph B. Hawkins
8500 Hidden River Parkway
Tampa, FL 33637

4. LEGAL BASIS FOR SUBMISSION
NDA 20393, Atrovent®, Boehringer Ingelheim

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Ipratropium Bromide

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 1-17-01
NC: 2-14-01

- Amendment: 5-7-01 (To add new testing facility of B&L).
- Major Amendment: 4-11-02 (Response to NA letter dated 7-3-01)
- Amendment: 4-15-02 (To provided current DS and DP methods)

FDA:
Accepted for filing: 1-18-01 (Acknowledgement letter: 2-14-01).
Bio deficiency letter: 5-30-01
NA letter: 7-3-01 (Chemistry + Labeling)

10. PHARMACOLOGICAL CATEGORY
Anticholinergic agent for perennial rhinitis

11. Rx or OTC:
Rx

12. RELATED IND/NDA/DMF(s):
See DMF Checklist

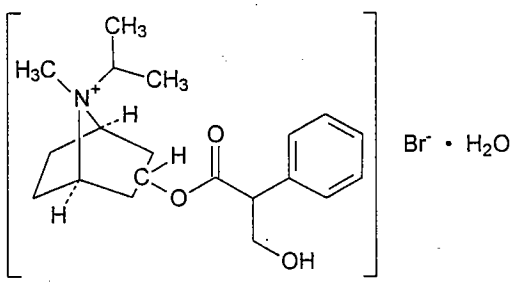
13. DOSAGE FORM
Nasal Spray

14. STRENGTH(s)
0.06%

15. CHEMICAL NAME AND STRUCTURE

Ipratropium bromide monohydrate [*66985-17-9*]
CAS number for anhydrous form is *22254-24-6*.

$C_{20}H_{30}BrNO_3-H_2O$
412.3659 anhydrous, 430.38 monohydrate



16. RECORDS AND REPORTS
N/A

17. A. GENERAL COMMENTS:

1. DMF ———for ———— is adequate per review completed on 6-21-01. No new information is submitted since this review.
2. Acceptance specifications for Ipratropium Bromide drug substance are not satisfactory.
3. Manufacturing process for the drug product is acceptable.
4. Information regarding container/closure became acceptable.
5. B&L has submitted adequate stability data to grant an expiration dating period of 24 months for the drug product.
6. EER: Acceptable as of 12-31-01.

7. B&L has not submitted a response to bio deficiency letter dated 5-30-01 yet. Based on this letter, Bioequivalency for the drug has not been demonstrated. B&L is being asked to submit response to deficiencies cited in May 30, 2001 letter.
8. FPL: Acceptable per review of 5-21-02 completed by A. Payne.

18. CONCLUSIONS AND RECOMMENDATIONS
NOT APPROVED. NA (Minor) Letter

19. REVIEWER: Mujahid L. Shaikh

DATE COMPLETED: 7-22-02
Revised on 7-23-02

APPEARS THIS WAY ON ORIGINAL

Redacted 43 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

cc: ANDA 76-103
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-625/MShaikh/7/23/02 Mujahid Shaikh 8/7/02
HFD-625/MSmela/7/24/02 Stan Adelt for M. Smela 8/7/02
HFD-617/PChen, Project Manager/8/6/02 Pat Chen 8/6/02

V:\FIRMSAM\BAUSCH\LTRS&REV\76103.RV2.doc
F/T by: gp/8/6/02

CHEMISTRY REVIEW - NOT APPROVABLE - MINOR

1. CHEMISTRY REVIEW NO. 3

2. ANDA # **76-103**

3. NAME AND ADDRESS OF APPLICANT
Bausch & Lomb Pharmaceuticals, Inc.(B&L)
Attention: Joseph B. Hawkins
8500 Hidden River Parkway
Tampa, FL 33637

4. LEGAL BASIS FOR SUBMISSION
NDA 20393, Atrovent®, Boehringer Ingelheim

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Ipratropium Bromide

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 1-17-01
NC: 2-14-01
Amendment: 5-7-01 (To add new testing facility of B&L).
Major Amendment: 4-11-02 (Response to NA letter dated 7-3-01)
Amendment: 4-15-02 (To provide current DS and DP methods)
* Minor Amendment: 8-29-02

FDA:
Accepted for filing: 1-18-01 (Acknowledgement letter: 2-14-01).
Bio deficiency letter: 5-30-01
NA letter: 7-3-01 (Chemistry + Labeling)
NA letter: 8-13-02 (Chemistry + labeling)

10. PHARMACOLOGICAL CATEGORY
Anticholinergic agent for perennial rhinitis

11. Rx or OTC:
Rx

12. RELATED IND/NDA/DMF(s):
See DMF Checklist

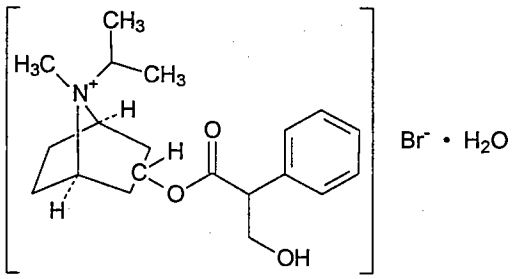
13. DOSAGE FORM
Nasal Spray

14. STRENGTH(s)
0.06%

15. CHEMICAL NAME AND STRUCTURE

Ipratropium bromide monohydrate [*66985-17-9*]
CAS number for anhydrous form is *22254-24-6.*

$C_{20}H_{30}BrNO_3-H_2O$
412.3659 anhydrous, 430.38 monohydrate



16. RECORDS AND REPORTS
N/A

17. A. GENERAL COMMENTS:

1. DMF ——— for ——————— is adequate per review completed on 8-27-02 by this reviewer.
2. Acceptance specifications for Ipratropium Bromide drug substance are satisfactory (CR # 2).
3. Information regarding container/closure became acceptable (CR # 2).
4. B&L has submitted adequate stability data to grant an expiration dating period of 24 months for the drug product.
5. EER: Acceptable as of 12-31-01.
6. B&L has not submitted a response to bio deficiency letter dated 5-30-01 yet. B&L stated in this amendment that they will response to bio deficiencies by the end of September 2002.

7. FPL: Acceptable per review of 5-21-02 completed by A. Payne.

18. CONCLUSIONS AND RECOMMENDATIONS
NOT APPROVED. NA (Minor) Letter

19. REVIEWER: Mujahid L. Shaikh

DATE COMPLETED: 9-10-02

APPEARS THIS WAY
ON ORIGINAL

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information from

CHEMISTRY REVIEW #3

38. Chemistry Comments to be Provided to the Applicant

ANDA: 76-103

APPLICANT: Bausch & Lomb Pharmaceuticals, Inc.

DRUG PRODUCT: Ipratropium Bromide Nasal Solution, 0.06%

The deficiencies presented below represent MINOR deficiencies.

1. Bioequivalence for the drug product has not been demonstrated. Please reply to this communication no earlier than your reply to the bioequivalence deficiencies dated May 30, 2001.

2. [redacted]

3. [redacted]

Sincerely yours,

Paul Schwoff for 9/17/02

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-103
ANDA DUP
DIV FILE
Field Copy

Endorsements:
HFD-625/MShaikh/9/10/02 Mujahid Shaikh 9/10/02
HFD-625/MSmela/9/10/02 M Smela 9/16/02
HFD-617/PChen, Project Manager Pat Chen 9/16/02

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F/T by: gp/9/13/02

CHEMISTRY REVIEW - NOT APPROVABLE - MINOR

5.1

1. CHEMISTRY REVIEW NO.4

2. ANDA # 76-103

3. NAME AND ADDRESS OF APPLICANT
Bausch & Lomb Pharmaceuticals, Inc.(B&L)
Attention: Joseph B. Hawkins
8500 Hidden River Parkway
Tampa, FL 33637

4. LEGAL BASIS FOR SUBMISSION
NDA 20393, Atrovent®, Boehringer Ingelheim

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Ipratropium Bromide

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 1-17-01
NC: 2-14-01
Amendment: 5-7-01 (To add new testing facility of B&L).
Major Amendment: 4-11-02 (Response to NA letter dated 7-3-01)
Amendment: 4-15-02 (To provide current DS and DP methods)
Minor Amendment: 8-29-02
* Amendment (Bio): 9-19-02
* Minor Amendment: 10-3-02 (Response to September 18, 2002 NA letter)

FDA:
Accepted for filing: 1-18-01 (Acknowledgement letter: 2-14-01).
Bio deficiency letter: 5-30-01
NA letter: 7-3-01 (Chemistry + Labeling)
NA letter: 8-13-02 (Chemistry + labeling)
NA letter: 9-18-02

10. PHARMACOLOGICAL CATEGORY
Anticholinergic agent for perennial rhinitis

11. Rx or OTC:
Rx

12. RELATED IND/NDA/DMF(s):
See DMF Checklist

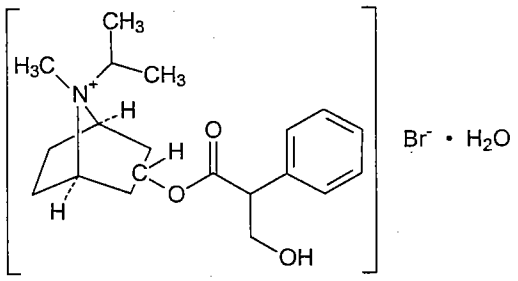
13. DOSAGE FORM
Nasal Spray

14. STRENGTH(s)
0.06%

15. CHEMICAL NAME AND STRUCTURE

Ipratropium bromide monohydrate [*66985-17-9*]
CAS number for anhydrous form is *22254-24-6*.

$C_{20}H_{30}BrNO_3$-H_2O
412.3659 anhydrous, 430.38 monohydrate



16. RECORDS AND REPORTS
N/A

17. A. GENERAL COMMENTS:

1. DMF ——— for ——————— is adequate per review completed on 8-27-02 by this reviewer.
2. Acceptance specifications for Ipratropium Bromide drug substance are satisfactory (CR # 2).
3. Information regarding container/closure became acceptable (CR # 2).

4. B&L has submitted adequate stability data to grant an expiration dating period of 24 months for the drug product.
5. EER: Acceptable as of 12-31-01.
6. B&L has submitted a response to bio deficiency letter dated 5-30-01 on September 19, 2002. This is pending review.
7. FPL: Acceptable per review of 5-21-02 completed by A. Payne.
8. Release and stability specifications became acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS
Chemistry Completed.

Bio review: Pending

19. REVIEWER: Mujahid L. Shaikh
DATE COMPLETED: 10-8-02

cc: ANDA 76-103
ANDA DUP
DIV FILE
Field Copy

Endorsements:
HFD-625/MShaikh/ mujahid shaikh 10/9/02
HFD-625/MSmela/ M Smela 10/9/02

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F/T by:

Bioequivalence signed off 3 at DBE on 1/23/03. HFS
M Smela 2/4/03
Reconsidered and signed off again by B. Davit on 3/14/03
M Smela 3/17/03

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CHEMISTRY REVIEW #4

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-103

BIOEQUIVALENCE REVIEWS

Ipratropium Bromide Solution
0.06% Nasal Spray, 42 µg/spray
ANDA #76-103
Reviewer: Mamata S. Gokhale
v:\firmsam\bausch\ltrs&rev\76103WAI.101

Bausch & Lomb Pharmaceuticals, Inc.
8500 Hidden River Parkway
Tampa, FL 33637
Submission Date: January ~~18~~ 17, 2001

Review of In Vitro Equivalence Data

BACKGROUND

1. The firm has submitted this ANDA pursuant to 21 CFR 314.94(a) and Section 505(j) of Federal Food, Drug and Cosmetic Act for its drug product, Ipratropium Bromide Nasal Spray, 0.06%. The reference-listed drug (RLD) is Atrovent® Nasal Spray, 0.06% (42 µg/spray, NDA #20-394) manufactured by Boehringer Ingelheim Pharmaceuticals Ltd.

2. Atrovent® (ipratropium bromide) Nasal Spray 0.06% is indicated for the symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in adults and children age 5 years and older (Electronic PDR, 2001).

3. The RLD is supplied as 15 mL of solution in a high density polyethylene bottle fitted with a metered nasal spray pump with a safety clip to prevent accidental discharge of the spray and a clear plastic dust cap. The 15 mL bottle is designed to deliver 165 sprays of 70 µL each (42 µg ipratropium bromide).

4. The recommended adult dose of Atrovent® Nasal Spray 0.06% is 2 sprays (84 µg) per nostril three or four times daily.

Requirements for waiver:

The demonstration of bioequivalence of aqueous nasal sprays may be based on: a) Q1 and Q2 sameness of the generic and innovator formulations, and b) equivalent performance of the test and reference product devices.

The comparative performance of the drug delivery devices of the test and reference products may be based on the following tests:

1. Unit Dose/Content Uniformity
2. Priming, loss of prime, and tail off
3. Droplet size distribution by at least 2 methods
4. Spray pattern
5. Plume geometry

Review of application:

Formulation: (not to be released under FOI)

Comparative compositions of the test and the reference products are as follows:

Ingredient	Test Product			[1]Reference Listed Drug		
	mg/mL	% w/v	mg/spray	mg/mL	% w/v	mg/spray
[2]Ipratropium bromide monohydrate, EP	0.60	0.06	0.042	0.60	0.06	0.042
Benzalkonium Chloride, NF	[redacted]					
[3]Edetate Disodium Dihydrate, NF	[redacted]					
[4]Sodium Chloride, NF	[redacted]					
Purified Water, USP	q.s. to 1 mL	-	-	q.s. to 1 mL	-	q.s. to 1 mL
Sodium Hydroxide, NF	pH adjuster	-	-	pH adjuster	-	-
Hydrochloric acid, NF	pH adjuster	-	-	pH adjuster	-	-

[1]Formulation of the reference-listed drug was obtained from the NDA 20-294 submission (Vol. 28.1). The valve size is 70 µL.
[2]Equivalent to 0.626 mg/mL of ipratropium bromide monohydrate, to achieve a final concentration of 0.6 mg/mL of ipratropium bromide on an anhydrous basis.
[3]The reference product contains Edetate Disodium which is same as Edetate Disodium Dihydrate (Merck Index, 12th edition, page 593).
[4]Quantity in the test product is within ±5% compared to the RLD.

Comment on Formulation:

The concentrations of the inactive ingredients for the test product are within the acceptable range (±5%) of the approved RLD. The formulation of the test product is qualitatively and quantitatively (Q1 and Q2) same as the RLD. The test product formulation is acceptable.

Comparability of Spray Devices:

[redacted], the manufacturer of the pump used for the RLD, has supplied Bausch and Lomb with a pump, which is essentially the same as that used for the sponsor's product. The pump used for Bausch and Lomb's ipratropium bromide Nasal Spray, 0.06%, is identical to the RLD pump with the exception of the closure thread finish and the amount of blue colorant in the closure gasket. The firm states that these differences have no potential to effect the pump performance. The firm has provided a comparison of the component parts for the pumps used in the test and reference products (see attachment). Based on this information, all components of the pump used for the test product are identical to those used for the RLD pump with the exception of the closure thread finish and the amount of blue colorant in the closure gasket.

Drug Products:

The in vitro performance data are based on **only one lot** of the test and reference products.

> Test: Ipratropium Bromide Nasal Spray 0.06%, 21, Lot #306081; Lot size ——
> Manufacturing date: 06/00, Assay: 100.6%
>
> Reference: Atrovent® Nasal Spray, 0.06%; Lot #869005A, manufactured by Boehringer Ingelheim; Expiry Date: 06/2001, Assay: 100.6%

Procedures and Information Applicable to All Tests:

All actuations of the nasal spray products were done using an automated actuator to actuate the nasal sprays in a reproducible manner. The automated actuator was a proprietary unit designed by ———— for nasal spray actuation. The actuation parameter setup for this systems were as follow:

> Dose Time: 20 msec. ± 1
> Return Time: 50 msec. ± 1
> Hold Time: 0.5 sec.
> Spray Force: 5.50 ± 0.05 kg

UNIT DOSE AND UNIFORMITY OF UNIT DOSE:

SOP C-1580-05, Archival Vol. 1.2, pp. 907

Testing was performed for 10 units each of reference and test product for all sprays including beginning (actuations #8-17), middle (actuations #86-95), and end (actuations #163-172) of use life. The amount actuated per spray was measured by a validated HPLC analysis (Method C-1579-04, archival volume 1.2, Section 15/Validation Report, pg. 665) with measurement by weight recorded as supportive data. A summary of the HPLC method validation is as follow:

> The peak area was linear over a range of ———— to ————. The limit of detection was ————. The LOQ was ————. The method exhibited acceptable specificity, accuracy and precision.

The firm notes that the test was not blinded because of mechanical actuation of the bottle, mechanical weighing of the bottle, and the fact that the scintillation vial was also weighed.

The firm applied the criteria for content uniformity for the test and reference products as set forth in the Division of Pulmonary Drug Products (HFD-570) draft CMC guidance (Guidance For Industry: Chemistry, Manufacturing and Controls Documentation for Inhalation Drug Products: MDIs and DPIs, June 26, 1998. The draft Guidance recommends a mean of 85-115% of the

label claim, and at the first tier (10 canisters) NMT one outside 80-120% at the first tier (10 canisters), and none outside 75-125% of the label claim.

Statistical Analysis:

The firm has analyzed data for the test and reference drug products by calculation of mean values and the variability of the data. The 90% confidence intervals for the ratio of true means (true mean of Test over true mean of Reference product) were constructed using Fieller's theorem. In addition, the firm has also calculated the f2 similarity factor for the percent label claim delivered for test and reference to provide another measure of the comparability of the data.

Results:

The firm has provided summary table giving the mean data for the beginning, middle and end actuations for the 10 bottles of test and reference products tested.

Based on the sponsor's calculations, mean delivery of the test product is 4.5% higher than the reference product at Actuations #8-17; 4.6% higher than the reference product at Actuations #86-95; and 4.5% higher than the reference product at Actuations #163-172. For the test and reference products no spray fell outside the 75-125% label claim range for the 10 bottles tested in this study.

Priming and Tail Off Characteristics:

The labeling of the test and reference products states: "Initial pump priming requires seven sprays of the pump. If used regularly as recommended, no further priming is required. If not used for more than 24 hours, the pump will require two sprays, or if not used for more than seven days, the pump will require seven sprays to reprime."

Priming: The firm has submitted data for sprays #1-7 for 10 bottles of the test product and 10 bottles of the reference product using HPLC assay. The firm has also submitted a graphic depiction of priming data demonstrating that by the 7th actuation of all products an acceptable dose was delivered for the 10 bottles tested for test and reference products. Mean delivery of the test product was 2.7% higher at spray #6 and 3.9% higher at spray #7 as compared to the RLD (archival vol. 1.1, pp. 75).

Prime Retention: The firm has conducted a study to test the ability of the test and reference pump system to maintain its prime after a given time period from last use. The pumps were tested for 1, 4, 7, 10 and 16 days after priming. The study demonstrated that after a non-use period some additional sprays are necessary before a therapeutic dose is delivered. At storage periods of 7 days or more, the test product requires less number of actuations to prime than the reference product (archival vol. 1.1, pp. 111-113).

Tail off: The firm has submitted data for sprays #173 and beyond for 10 bottles of the test product and 10 bottles of the reference product using HPLC assay. There were ample therapeutic sprays beyond #165 to allow for periods when the product is not used, and to allow for the cleaning of the actuator and repriming.

Results: Based on the study results the tested test and reference products delivered the labeled number of full medication doses. The tail off pattern of the test product is no more erratic that the reference product.

Comments on the Unit Dose Data:

The firm determined comparative unit dose data based on **single lots** of the test and reference products. The in vitro studies were conducted approximately a year after the issuance of the draft guidance "*Guidance for Industry Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*" issued in June 1999. The firm has not cited this guidance.

The draft Nasal BA/BE guidance recommends in vitro equivalence based on **three lots** of the test and reference products, because the proposed method of evaluation takes into consideration the relative within-lot and lot-to-lot variations of the test and reference products. The reviews of all applications submitted after the issuance of guidance, which also contain in vitro studies conducted after the issuance of the guidance, are being evaluated based on **three lots'** data.

The statistical method given in the guidance is still under development. However the Division of Bioequivalence is currently evaluating generic nasal sprays based on relative variability of test and reference products. Therefore, data submitted by Bausch and Lomb do not lend themselves to the DBE's current approach as well as the statistical methodology given in the guidance.

DROPLET SIZE DISTRIBUTION

SOP C-1586-01, Archival Vol. 1.3, pp. 920
SOP 73-088-06, Archival Vol. 1.3, pp. 981

Testing was performed on the ———————, with one spray per test per distance (duplicate testing per interval). Testing was performed on 10 units each of the reference and test products at beginning (sprays #8-13), middle (sprays #86-91), and end (sprays #163-168) of use life. Distances from the laser beam were 3, 5 and 7 cm.

Two instruments were used in conjunction with each other to make the analysis completely automated. The ——————————— is the device that mechanically actuates the nasal spray into the ———————, the laser diffractor that reads the droplet size.

The firm states that this test was not blinded because the actuation of spray pumps for both the test and reference products was automated, and all analyses were performed by the instrument. There was no human intervention. Automated actuation by definition involves the same dose time, return time, hold time and force for the test and reference products as defined in the Methods C-1586-01, 73-088-06 and 73-088-06 (Section 15, Vol. 1.3).

Data for the test and reference products were analyzed by calculation of mean values and the variability of the data. The 90% confidence intervals for the ratio of true means (true mean of Test over true mean of Reference product) were constructed using Fieller's theorem. In addition, the firm has also calculated the f2 similarity factor was calculated for the % of droplets between 10 and 500 μm and % of droplets greater than 500 μm to provide another measure of the comparability of the data.

Comments on the Droplet Size Distribution:

1. As mentioned above the in vitro testing was performed on single lots of test and reference products. Therefore, the comment given for the Unit dose data is applicable to the Droplet Size Distribution data.

2. With regard to the testing procedure, the firm does not state the stage of plume formation for which the D50 and SPAN data were collected. In the absence of this information, it is difficult to determine if these data represent fully formed sprays.

3. Based on the above comments, the droplet size distribution data are unacceptable. The firm should repeat this test using three lots of the test and reference products. The test should be performed at the beginning, middle and end of product life and at three distances between the orifice and the laser beam. For each spray, the firm should provide D10, D50, D90 and SPAN data for the following three stages of the plume formation based on obscuration (or %transmission) of the laser beam:

   (1) Plume formation characterized by increase in obscuration.

   (2) Fully formed plume characterized by a period of relatively stable obscuration.

   (3) Dissipating plume characterized by decrease in obscuration relative to the stable obscuration.

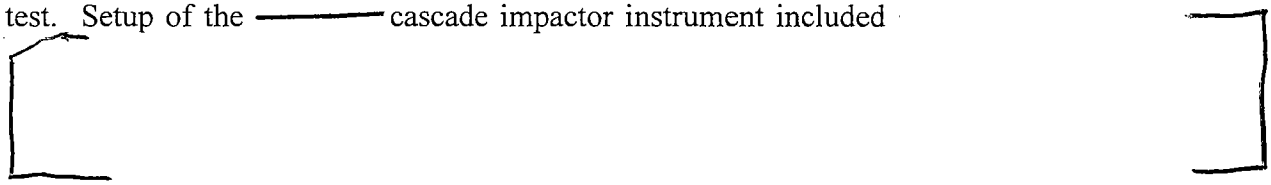
The firm should provide representative ($\geq$ 20%) graphs of obscurations vs. time (msec). These graphs should also contain plots of D10, D50 and D90 vs. time data. Furthermore, if possible data regarding the duration of the "fully formed" plume as well as entire spray of the test and reference products should also be submitted.

CASCADE IMPACTION:

Nasal Instrument Procedure NIP-2000-001 Archival Vol. 1.3, pp 1046

The ——— cascade impactor selectively segregates particles less than about 10 microns in diameter. Cascade impaction is performed to determine that there is not an excess mass of fines in the test product relative to the RLD.

Testing was performed on 10 units each of the test and reference drug products at beginning (sprays #8-17) and end (sprays #163-172) of the product use life. There were 10 actuations per test. Setup of the ——— cascade impactor instrument included



1579-04, archival volume 1.2, Section 15/Validation Report, pg. 665). For the HPLC method, the limit of detection was——— and the limit of quantification was ———. Testing was conducted according to Nasal Instrument Procedure NIP-2000-001.

Testing was performed in a blinded manner to hide the identity of test and RLD products from the analyst. For this test, the units were manually actuated (10 actuations per test) for all testing for the test and reference products.

The procedure used for blinding test and RLD products from the analyst is fully described in the blinding procedure description (Nasal Instrument Procedure NIP-2000-001, pp. 1047, archival vol. 1.3).

Comments on Cascade Impaction Data

As mentioned above the in vitro testing was performed on **single lots** of test and reference products. Therefore, the comment given for the Unit Dose data is applicable to the Cascade Impaction data.

SPRAY PATTERN:

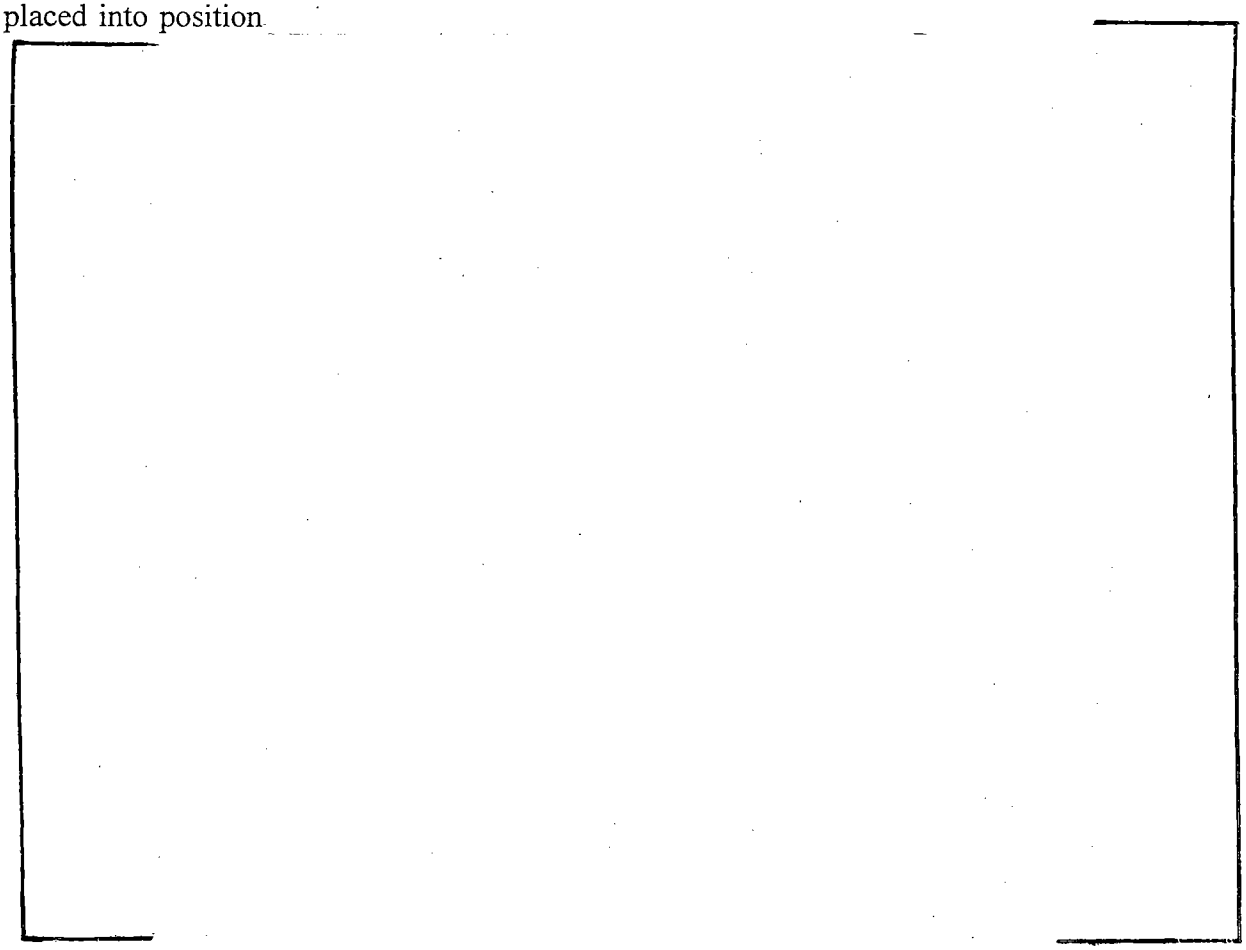
SOP C-1587-03, Archival Vol. 1.3, pp. 931,
SOP 73-108-02, Archival Vol. 1.3, pp. 1011
SOP 73-147-00, Archival Vol. 1.3, pp. 1038

Spray pattern testing was done on 10 units each of test and reference products at 3, 4, and 5 cm distances from nozzle to plate, and tested at beginning (8th actuation) and end (163rd actuation) of the use life. Duplicate testing was conducted for each of the three distances — 1 spray at 3 cm, 1 spray at 4 cm, 1 spray at 5 cm. For visualization of the spray pattern on the plate, the TLC plate ——— was evenly sprayed with ——— solution (a pH sensitive indicator), turning the plate a pale orange color.

The image was read using an UV light at 254 nm, leaving a green pattern wherever the formulation rests on the black background of the plate. Color images were then digitized and analyzed by the ———————————— This system automatically determines the longest and shortest radii and calculates the corresponding spray angles, the elliptical ratio (longest/ shortest angle), and the ovality ratio (longest/shortest diameter).

The test was not blinded as all units were mechanically actuated with no analyst mechanical intervention on the results. The results are measured by computer.

Operation of ————————————: Once the pattern is detected on a TLC plate and placed into position



Statistical Analysis: Same as above.

Comments on Spray Pattern Data

As mentioned above, the in vitro testing was performed on **single lots** of test and reference products. Therefore, the comment given for the Unit dose data is applicable to the Spray Pattern data.

PLUME GEOMETRY by FREEZE-FRAME PHOTOGRAPHY:

SOP for Blinding Archival Vol. 3, pp. 1011
Nasal Instrument Procedure NIP-2000-006 Archival Vol. 1.3, pp 1057

The firm has conducted this test as per the May 1999 draft CMC guidance for Nasal Spray Drug Products.

The freeze-frame photography for 10 units each of the test and reference products was captured photographically at the beginning of the product use life. At least, six time delays (0.0167, 0.0334, 0.0501, 0.0668, 0.0835, 0.1002 seconds) were used.

Testing was performed in a blinded manner to hide the identity of test and reference products from the analyst. The units were manually actuated 7 times to assure prime with the 8th spray being the test. Testing was conducted according to Nasal Instrument Procedure NIP-2000-006 (Section 15, Vol. 1.3, pp.1058-1062). Each plume was sprayed in an upright, stationary position. As it was being filmed, the spray evolved and dissipated in front of a grid graduated in inches. The room in which testing was performed was ventilation free and sound proof to eliminate any currents or vibration of droplets. There was no exhaust hood above the plume.

The plume angle was measured using [redacted]. The program has a function built into it that allows an analyst to [redacted]

Individual photographs per bottle are provided in volumes 1.13 and 1.14.

Comments on Plume Geometry Data

As mentioned above the in vitro testing was performed on **single lots** of test and reference products. Therefore, the comment given for the Unit dose data is applicable to the Plume Geometry data.

Additionally, the firm should be advised that plume measurements at 3 time-delays 0.033, 0.066 and 0.100 seconds may be sufficient, instead of the 6 time-delays 0.0167, 0.0334, 0.0501, 0.0668, 0.0835, 0.1002 seconds used in the above study.

Deficiencies:

1 On comparability of spray devices:

The firm is asked to provide technical/engineering drawings of the test and reference pumps.

2 All in vitro tests:

The firm used single lots of the test and reference products to determine comparative data for all in vitro testing. The in vitro studies were conducted according to the CDER Guidance For Industry: *Chemistry, Manufacturing and Controls Documentation for Inhalation Drug Products: MDIs and DPIs*, June 26, 1998.

The draft guidance *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* was issued in June 1999. The firm conducted in vitro studies approximately a year after the issuance of this guidance.

The June 1999 draft guidance recommends in vitro equivalence based on three lots of the test and reference products, because the proposed method of in vitro evaluation takes into consideration the relative within lot and lot-to-lot variations of the test and reference products.

The firm's in vitro performance testing is therefore incomplete. The firm should be advised to submit data from three batches of the test and reference products for all in vitro tests.

3 Droplet size distribution:

With regard to the testing procedure, the firm has not stated the stage of plume formation for which the D50 and SPAN data were collected. Thus, it is difficult to determine if these data represent fully formed sprays.

The firm should repeat this test using three lots of the test and reference products. The test should be performed at the beginning, middle and end of product life and at three distances between the orifice and the laser beam. For each spray, the firm should submit D10, D50, D90 and SPAN data for the following three stages of the plume formation based on obscuration (or %transmission) of the laser beam:

(1) Plume formation characterized by increase in obscuration.
(2) Fully formed plume characterized by a period of relatively stable obscuration.
(3) Dissipating plume characterized by decrease in obscuration relative to the stable obscuration.

These data should be accompanied by representative ($\geq$ 20%) graphs of obscurations vs. time (msec). These graphs should also contain plots of D10, D50 and D90 vs. time data. Furthermore, if possible data regarding the duration of the "fully formed" plume as well as entire spray of the test and reference products should also be submitted.

Recommendation:

The in vitro performance testing conducted by Bausch and Lomb on its Ipratropium Bromide Nasal Spray, 0.06%, Lot #306081 comparing it with the reference product, Atrovent® Nasal Spray, 0.06%, Lot #869005A has been found incomplete due to the deficiencies mentioned above.

The firm should be informed of the comments and recommendation.

Mamata S. Gokhale, Ph.D. Mamata Gokhale 5/23/01
Division of Bioequivalence

RD INITIALED BDAVIT
FT INITIALED BDAVIT Barbara M Davit Date 5/24/01

Concur: N Patwardhan Date 5/24/2001
for Dale P. Conner, Pharm.D. Director
Division of Bioequivalence

cc: ANDA# 76-103 (original, duplicate), Davit, HFD-658, Gokhale, HFD-658, Drug File, Division File

APPEARS THIS WAY ON ORIGINAL

CC: ANDA # 76-103
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer: M. Gokhale
HFD-658/ TL: B. Davit

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Printed in final on 5/11/2001

Endorsements: (Final with Dates)
HFD-658/ M. Gokhale MSK 5/23/01
HFD-655/ Gur J.P. Singh GJPS 5/24/01
HFD-658/ B. Davit Bhd 5/24/01
HFD-650/ D. Conner for Dec 5/30/2001
HFD-617/ S. Mazzella

BIOEQUIVALENCY – Incomplete

Submission Date: 1/~~18~~17/2001

Biowaiver (WAI/OT)

Strength: 0.06%
Outcome: IC

Outcome Decisions:

IC – Incomplete

WinBio Comments:

- ~~Biowaiver request~~ is incomplete

The in vitro testing

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA:76-103 APPLICANT: Bausch & Lomb Pharmaceuticals, Inc.

DRUG PRODUCT: Ipratropium Bromide Nasal Spray 0.06%

The Division of Bioequivalence has completed its review of your application acknowledged on the cover sheet. The following deficiencies have been identified:

1. All in vitro tests:

You have used single lots of the test and reference products to determine comparative data for all in vitro testing. The in vitro studies were conducted approximately a year after the issuance of the draft guidance "*Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*" issued in June 1999. The draft guidance recommends in vitro equivalence based on three lots of the test and reference products, because the proposed method of evaluation takes into consideration the relative within-lot and lot-to-lot variations of the test and reference products.

Your in vitro performance testing is therefore unacceptable. You are advised to submit data using three lots of the test and reference products for the following in vitro tests:

1. Unit Dose/Content Uniformity
2. Priming, loss of prime, and tail off
3. Droplet size distribution by at least two methods
4. Spray pattern
5. Plume geometry

2. Droplet size distribution:

With regard to the testing procedure, you have not stated the stage of plume formation for which the D50 and SPAN data were collected. When you repeat this test using three lots of the test and reference products, it should be performed at the beginning, middle and end of product life and at three distances between the orifice and the laser beam. For each spray, please submit D10, D50, D90 and SPAN data for the following three stages of the plume formation based on obscuration (or %transmission) of the laser beam

(1) Plume formation characterized by increase in obscuration.
(2) Fully formed plume characterized by a period of relatively stable obscuration.
(3) Dissipating plume characterized by decrease in obscuration relative to the stable obscuration.

The above data should be accompanied by representative ($\geq$ 20%) graphs of obscurations vs. time (msec). These graphs should also contain plots of D10, D50 and D90 vs. time data. Furthermore, if possible, please submit data regarding the duration of the "fully formed" plume of test and reference products.

Additionally, the Agency recommends the following:

1. **Comparability of spray devices:**
   Please submit technical/engineering drawings of the test and reference pumps.

2. **Plume geometry data:**
   The Agency recommends using only 3 time-delays - e.g. 0.033, 0.066 and 0.100 seconds, instead of the 6 time-delays - 0.0167, 0.0334, 0.0501, 0.0668, 0.0835, 0.1002 seconds used in your Plume Geometry study.

3. **Data submission:**
   Please submit data electronically for the lots of the test and reference products in spread-sheet format as attached herewith. Test/Reference ratios based on geometric means are also requested. Please note that the minimum ANDA batch size should be 5000 bottle. Please indicate the number of bottles in each lot of the test product.

Sincerely yours,

for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Ipratropium Bromide Solution
0.06% and 0.03% Nasal Spray
ANDA #76-103 (0.06%) and 76-025 (0.03%)
Reviewer: Gur J.P. Singh
File #76103A.901 and 76025A.901

Bausch & Lomb
8500 Hidden River Parkway
Tampa, FL 33637
Submission Date: Sept. 26, 2001

Review of an ANDA Amendment

On January 18, 2001, the firm submitted comparative in vitro performance data on its ipratropium bromide nasal spray (0.06% and 0.03%) and the innovator product, Atrovent® Nasal Spray 0.06%. The Division of Bioequivalence completed its review of the in vitro data on May 11, 2001. Based on that review the firm was informed of the following deficiencies:

1. All in vitro tests:

You have used single lots of the test and reference products to determine comparative data for all in vitro testing. The in vitro studies were conducted approximately a year after the issuance of the draft guidance "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action" issued in June 1999. The draft guidance recommends in vitro equivalence based on three lots of the test and reference products, because the proposed method of evaluation takes into consideration the relative within-lot and lot-to-lot variations of the test and reference products.

Your in vitro performance testing is therefore unacceptable. You are advised to submit data using three lots of the test and reference products for the following in vitro tests:

1. *Unit Dose/Content Uniformity*
2. *Priming, loss of prime, and tail off*
3. *Droplet size distribution by at least two methods*
4. *Spray pattern*
5. *Plume geometry*

2. Droplet size distribution:

With regard to the testing procedure, you have not stated the stage of plume formation for which the D50 and SPAN data were collected. When you repeat this test using three lots of the test and reference products, it should be performed at the beginning, middle and end of product life and at three distances between the orifice and the laser beam. For each spray, please submit D10, D50, D90 and SPAN data for the following three stages of the plume formation based on obscuration (or %transmission) of the laser beam:

(1) Plume formation characterized by increase in obscuration.
(2) Fully formed plume characterized by a period of relatively stable obscuration.
(3) Dissipating plume characterized by decrease in obscuration relative to the stable obscuration.

The above data should be accompanied by representative (≥ 20%) graphs of obscurations vs. time (msec). These graphs should also contain plots of D10, D50 and D90 vs. time data. Furthermore, if possible, please submit data regarding the duration of the "fully formed" plume of test and reference products.

Additionally, the Agency recommends the following:

1. ***Comparability of spray devices:*** *Please submit technical/engineering drawings of the test and reference pumps.*

2. ***Plume geometry data:*** *The Agency recommends using only 3 time-delays - e.g. 0.033, 0.066 and 0.100 seconds, instead of the 6 time-delays - 0.0167, 0.0334, 0.0501, 0.0668, 0.0835, 0.1002 seconds used in your Plume Geometry study.*

3. ***Data submission:*** *Please submit data electronically for the lots of the test and reference products in spread-sheet format as attached herewith. Test/Reference ratios based on geometric means are also requested. Please note that the minimum ANDA batch size should be 5000 bottle. Please indicate the number of bottles in each lot of the test product.*

On August 10, 2001, the firm held a tele-conference with the Division representative to clarify some of the above deficiencies. In the current amendment, the firm has submitted (1) its proposal for determination of droplet size distribution of the test product, and (2) requested a copy of the spreadsheet-format template for submission of in vitro data.

Comments

1. ***Analysis of Droplet Size Distribution:*** Droplet size distribution will be determined by laser diffraction at 3, 5 and 7 cm distances from the orifice and at beginning, middle and end sectors of product use. At each of the distance/sector combination, the firms will determine droplet size distribution for three regions of the spray plume. These regions will be determined based on % obscuration of the laser light. Of the three regions, Plume Formation is characterized by a rise in % obscuration, the Fully Formed Plume by stable obscuration, and Plume Dissipation by decline in % obscuration. In each of the three regions, samples will be taken every two msec over a period of 120 msec. The values reported for a given stage of plume life will represent average of the 2-msec samples taken over the entire region.

   The firm's proposal is acceptable. The firm does not need to submit standard deviation and % RSD for parameter values representing single sprays. Instead, the single D10, D50, D90 and SPAN values for the stable region of each spray should be submitted in the attached spreadsheet format. The criteria for identifying the initiation and termination of the stable region should be specified in the protocol/SOP. Parametric data for the initial (plume formation) and end (plume dissipation) sections of the plume need not to be submitted. The requested ≥ 20% time-history plots over the entire life of the spray

(instrument onset to offset) should contain the % obscuration, D10, D50 and D90 data for a given spray on the same plot. Each plot should be labeled to identify the stable region of the plume, distance, product life stage, and the product, batch number and bottle number. Plots of SPAN data are not essential.

2. The spreadsheet format template requested by the firm is attached herewith.

Recommendation

The firm's proposal for droplet size distribution testing is acceptable. It should be informed of the comments #1. In addition, the firm should be provided with a copy of the attached spreadsheet format.

Gur Jai Pal Singh, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR Date 11/20/2001

Concur: Date 12/11/2001

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA: 76-103 and 76-025 APPLICANT: Bausch & Lomb

DRUG PRODUCT: Ipratropium Bromide Nasal Sprays 0.06% and 0.03%

The Division of Bioequivalence has completed its review of your application acknowledged on the cover sheet. It has the following comments:

Analysis of Droplet Size Distribution: Your proposal indicated that you will determine droplet size distribution by laser diffraction at 3, 5 and 7 cm distances from the orifice and at the beginning, middle and end sectors of product use. At each of the distance/sector combination, you will determine droplet size distribution for three regions of the spray plume. These regions will be determined based on % obscuration of the laser light. Of the three regions, Plume Formation is characterized by a rise in % obscuration, the Fully Formed Plume by stable obscuration, and Plume Dissipation by decline in % obscuration. In each of the three regions, samples will be taken every two msec over a period of approximately 120 msec. The parameter (i.e., D50, D90..) values reported for a given stage of plume life will represent average of the 2-mec samples taken over the entire region.

Your proposal is acceptable. However please note that you do not need to submit standard deviation and % RSD for parameter values representing single sprays. Instead, the single D10, D50, D90 and SPAN values for the stable region of each spray should be submitted in the attached spreadsheet format. The criteria for identifying the initiation and termination of the stable region should be specified in the protocol/SOP. Parametric data for the initial (plume formation) and end (plume dissipation) sections of the plume need not to be submitted. The requested ≥ 20% time-history plots over the entire life of the spray (instrument onset to offset) should contain the % obscuration, D10, D50 and D90 data for a given spray on the same plot. Each plot should be labeled to identify the stable region of the plume, distance, product life stage, and the product, batch number and bottle number. Plots of SPAN data are not essential.

Spreadsheet Format. The spreadsheet template requested in your correspondence is attached herewith.

Sincerely yours,

for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA # 76-103 and 76-025
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Reviewer
HFD-655/ Team Leader

\\CDS008\WP51F99\FIRMSAM\BAUSCH\LTRS&REV\76103A.901.doc
and 76025A.901.doc

Endorsements: (Final with Dates)
HFD-655/ Gur J.P. Singh 10-31-01
HFD-655/ S. Nerurkar 11/20/01
HFD-650/ D. Conner 12/11/2001

BIOEQUIVALENCY - Acceptable **Submission Date: Sept. 26, 2001**

Study Amendment (STA) ✓ **Strength: 0.06%**
Outcome: ~~AC~~ IC

Study Amendment (~~STA~~) NC X **Strength: 0.03%**
Outcome: ~~AC~~ IC

Draft Format Tables
for
Comparative In Vitro Performance Data
for
Oral Inhalation Aerosols, Nasal Aerosols and Nasals Sprays

GJPS 5/8/00

Table 1: Unit Dose Data*....(ANDA # .....)

Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p* (Tvs.R)**
TEST	1	Beg														
		Mid														
		End														
	2	Beg														
		Mid														
		End														
	3	Beg														
		Mid														
		End														
REF	1	Beg														
		Mid														
		End														
	2	Beg														
		Mid														
		End														
	3	Beg														
		Mid														
		End														

** For Nasal sprays, Beginning (Beg) and End only.*

*** Based on combined data of three lots, separately at Beg, Middle (Mid) and End*

Table 2: Priming Data....(ANDA # .....)

(Similar table for Repriming Data, where applicable per REF labeling)

Product	Lot #	Actuation #	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p* (Tvs.R)**
TEST	1	1														
		2														
		3														
		To the first full medication dose														
	2	1														
		2														
		3														
		To the first full medication dose														
	3	1														
		2														
		3														
		To the first full medication dose														
REF	1	1														
		2														
		3														
		To the first full medication dose														
	2	1														
		2														
		3														
		To the first full medication dose														
	3	1														
		2														
		3														
		To the first full medication dose														

*** Based on combined data of three lots.*

2

Table 3: Tail Off Data....(ANDA # .....)

Product	Lot #	Actuation #	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p (Tvs.R)**
TEST	1	Last labeled (LL)														
		LL + 1														
		LL + 2														
		⮟														
		Depletion														
	2	Last labeled (LL)														
		LL + 1														
		LL + 2														
		⮟														
		Depletion														
	3	Last labeled (LL)														
		LL + 1														
		LL + 2														
		⮟														
		Depletion														
REF	1	Last labeled (LL)														
		LL + 1														
		LL + 2														
		⮟														
		Depletion														
	2	Last labeled (LL)														
		LL + 1														
		LL + 2														
		⮟														
		Depletion														
	3	Last labeled (LL)														
		LL + 1														
		LL + 2.														
		⮟														
		Depletion														

*** Based on combined data of three lots.*

3

Table 4: Cascade Impaction Data....(ANDA # .....)

(For nasal aerosols & nasal sprays, data may be combined into three groups per the draft Nasal BA/BE Guidance)
(Table format is based on the Andersen Cascade Impactor. It should be modified appropriately for other devices)

				Drug Deposition on (Mass Units)										
PROD	SECTOR	Lot #	Can #	Valve Stem	Act.	Throat	S-0	S-1	S-2	S-3	S-4	S-5	S-6	S-7	Filter
			1												
			2												
			3												
			4												
			5												
		1	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
			4												
TES	BEG		5												
		2	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
			4												
			5												
		3	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
		Grand	Mean												
		Grand	%CV												

4

PROD	SECTOR	Lot #	Can #	Drug Deposition on (Mass Units) Valve Stem	Act.	Throat	S-0	S-1	S-2	S-3	S-4	S-5	S-6	S-7	Filter
			1												
			2												
			3												
			4												
			5												
		1	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
TES	END		4												
			5												
		2	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
			4												
			5												
		3	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
		Grand	Mean												
		Grand	%CV												

TeS/REF (Grand Mean)	BEG END
*p (Tvs.R)***	BEG END

*** Based on combined data of three lots, separately at Beg & End*

5

Table 4: Cascade Impaction Data....(ANDA # .....)

nasal aerosols & nasal sprays, data may be combined into three groups per the draft Nasal BA/BE Guidance)
able format is based on the Andersen Cascade Impactor. It should be modified appropriately for other devices)

				Drug Deposition on (Mass Units)											
PROD	SECTOR	Lot #	Can #	Valve Stem	Act.	Throat	S-0	S-1	S-2	S-3	S-4	S-5	S-6	S-7	Filter
			1												
			2												
			3												
			4												
			5												
		1	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
			4												
REF	BEG		5												
		2	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
			4												
			5												
		3	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
		Grand	Mean												
		Grand	%CV												

6

PROD	SECTOR	Lot #	Can #	Drug Deposition on (Mass Units) Valve Stem	Act.	Throat	S-0	S-1	S-2	S-3	S-4	S-5	S-6	S-7	Filter
			1												
			2												
			3												
			4												
			5												
		1	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
REF	END		4												
			5												
		2	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
			4												
			5												
		3	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
		Grand	Mean												
		Grand	%CV												

7

Table 5: Particle Sizing by Laser Diffraction....(ANDA # .....)

Note: Laser diffraction data for each of the three phases (Initial, Full and Dissipation) of plume should be reported at Beginning, Middle and End of product use life.

D50 *(Comparable tables for D10 and D90 are also requested)*

Distance	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p (Tvs.R)**
(3, 5 and 7 cm are provided as examples. Other distances may be appropriate for specific products)			Beg														
		1	Mid														
			End														
			Beg														
	TEST	2	Mid														
			End														
			Beg														
		3	Mid														
			End														
3 cm																	
			Beg														
		1	Mid														
			End														
			Beg														
	REF	2	Mid														
			End														
			Beg														
		3	Mid														
			End														

*** Based on combined data of three lots, separately at Beg, Mid & End*

8

D50 *(Comparable tables for D10 and D90 are also requested)*

Distance (Example)	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p* (Tvs.R)**
		1	Beg														
			Mid														
			End														
	TEST	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														
5 cm																	
		1	Beg														
			Mid														
			End														
	REF	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														

*** Based on combined data of three lots, separately at Beg, Mid & End*

9

D50 *(Comparable tables for D10 and D90 are also requested)*

Distance (Example)	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p* (Tvs.R)**
		1	Beg														
			Mid														
			End														
	TEST	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														
7 cm																	
		1	Beg														
			Mid														
			End														
	REF	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														

*** Based on combined data of three lots, separately at Beg, Mid & End***

10

Table 5: Particle Sizing by Laser Diffraction....(ANDA # .....)

SPAN [(D90-D10)/D50]

Distance (Example)	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p* (Tvs.R)**
		1	Beg														
			Mid														
			End														
	TEST	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														
3 cm																	
		1	Beg														
			Mid														
			End														
	REF	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														

*** Based on combined data of three lots, separately at Beg, Mid & End*

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SPAN [(D90-D10)/D50]

Distance (Example)	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p* (Tvs.R)**
		1	Beg														
			Mid														
			End														
	TEST	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														
5 cm																	
		1	Beg														
			Mid														
			End														
	REF	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														

*** Based on combined data of three lots, separately at Beg, Mid & End***

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SPAN [(D90-D10)/D50]

Distance (Example)	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p* (Tvs.R)**
		1	Beg														
			Mid														
			End														
		2	Beg														
	TEST		Mid														
			End														
		3	Beg														
			Mid														
			End														
7 cm																	
		1	Beg														
			Mid														
			End														
		2	Beg														
	REF		Mid														
			End														
		3	Beg														
			Mid														
			End														

*** Based on combined data of three lots, separately at Beg, Mid & End***

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Table 6: Spray Pattern Data....(ANDA # .....)

Dmin

Distance	Product	Lot #	Lot #	Stage	Bottle/Can # 1 2 3 4 5 6 7 8 9 10	Mean	%CV	Test/Ref	p (Tvs.R)**
(3, 5 and 7 cm are provided as examples. Other distances may be appropriate for specific products)		1	1	Beg					
				End					
	TEST	2	2	Beg					
				End					
		3							
			3	Beg					
				End					
3 CM		1	1	Beg					
				End					
	REF	2	2	Beg					
				End					
		3	3	Beg					
				End					

*** Based on combined data of three lots, separately at Beg & End*

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Dmin

Distance (Example)	Product	Lot #	Lot #	Stage	Bottle/Can # 1 2 3 4 5 6 7 8 9 10	Mean	%CV	Test/Ref	p (Tvs.R)**
		1	1	Beg					
				End					
	TEST	2	2	Beg					
				End					
		3							
			3	Beg					
				End					
5 CM									
		1	1	Beg					
				End					
	REF	2	2	Beg					
				End					
		3							
			3	Beg					
				End					

*** Based on combined data of three lots, separately at Beg & End*

15

Dmin

Distance (Example)	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p (Tvs.R)**
		1	Beg														
			End														
	TEST	2	Beg														
			End														
		3	Beg														
			End														
10 Cm																	
		1	Beg														
			End														
	REF	2	Beg														
			End														
		3	Beg														
			End														

*** Based on combined data of three lots, separately at Beg & End*

16

Table 6: Spray Pattern Data....(ANDA # .....)

Dmax

Distance (Example)	Product	Lot #	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p* (Tvs.R)**
		1	1	Beg														
				End														
	TEST	2	2	Beg														
				End														
		3																
			3	Beg														
				End														
3 CM																		
		1	1	Beg														
				End														
	REF	2	2	Beg														
				End														
		3	3	Beg														
				End														

*** Based on combined data of three lots, separately at Beg & End*

17

Dmax

Distance (Example)	Product	Lot #	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p (Tvs.R)**
		1	1	Beg														
				End														
	TEST	2	2	Beg														
				End														
		3	3	Beg														
				End														
5 CM																		
		1	1	Beg														
				End														
	REF	2	2	Beg														
				End														
		3																
			3	Beg														
				End														

*** Based on combined data of three lots, separately at Beg & End***

18

Dmax

Distance (Example)	Product	Lot #	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref
		1	1	Beg													
				End													
	TEST	2	2	Beg													
				End													
		3	3	Beg													
				End													
10 Cm																	
		1	1	Beg													
				End													
	REF	2	2	Beg													
				End													
		3	3	Beg													
				End													

*** Based on combined data of three lots, separately at Beg & End*

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Table 6: Spray Pattern Data....(ANDA # .....)

Ovality Ratio (Dmax/Dmin)

Distance	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p* (Tvs.R)**
		1	Beg														
			End														
	TEST	2	Beg														
			End														
		3	Beg														
			End														
3 CM																	
		1	Beg														
			End														
	REF	2	Beg														
			Mid														
			End														
		3	Beg														
			End														

*** Based on combined data of three lots, separately at Beg & End***

20

Ovality Ratio

Distance	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p (Tvs.R)*
		1	Beg														
			End														
	TEST	2	Beg														
			End														
		3	Beg														
			End														
5 CM																	
		1	Beg														
			End														
	REF	2	Beg														
			End														
		3	Beg														
			End														

*** Based on combined data of three lots, separately at Beg & End***

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Ovality Ratio

Distance	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	** *Based on combined data of three lots, separately at Beg & End*
		1	Beg														
			End														
	TEST	2	Beg														
			End														
		3	Beg														
			End														
10 Cm																	
		1	Beg														
			End														
	REF	2	Beg														
			End														
		3	Beg														
			End														

22

Table 7: Plume Geometry Data....(ANDA # .....)

Plume Width

PROD	LOT	Time* (Sec)	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	PROD	LOT	Time* (Sec)	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p* (Tvs.R)**
		0.015															0.015														
		0.030															0.030														
		0.045															0.045														
	1	0.060														1	0.060														
		0.090															0.090														
		0.120															0.120														
		.															.														
		0.015															0.015														
		0.030															0.030														
TEST	2	0.045													REF	2	0.045														
		0.060															0.060														
		0.090															0.090														
		0.120															0.120														
		.															.														
		0.015															0.015														
		0.030															0.030														
	3	0.045														3	0.045														
		0.060															0.060														
		0.090															0.090														
		0.120															0.120														
		.															.														

** Postactuation delay times noted here may need optimization based on nasal spray plume characteristics. Different delay times may be appropriate for pressurized aerosol products. For additional information, see Nasal BA/BE Guidance*

*** Based on combined data of three lots*

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Table 7: Plume Geometry Data....(ANDA # .....)

Plume Length

PROD	LOT	Time* (Sec)	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p (Tvs.R)**
		0.015														
		0.030														
		0.045														
	1	0.060														
		0.090														
		0.120														
		.														
		0.015														
		0.030														
TEST	2	0.045														
		0.060														
		0.090														
		0.120														
		.														
		0.015														
		0.030														
	3	0.045														
		0.060														
		0.090														
		0.120														
		.														

PROD	LOT	Time* (Sec)	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p (Tvs.R)**
		0.015														
		0.030														
		0.045														
	1	0.060														
		0.090														
		0.120														
		.														
		0.015														
		0.030														
REF	2	0.045														
		0.060														
		0.090														
		0.120														
		.														
		0.015														
		0.030														
	3	0.045														
		0.060														
		0.090														
		0.120														
		.														

** Postactuation delay times noted here may need optimization based on nasal spray plume characteristics. Different delay times may be appropriate for pressurized aerosol products. For additional information, see Nasal BA/BE Guidance*

*** Based on combined data of three lots*

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Table 7: Plume Geometry Data....(ANDA # .....)

Plume Angle

PROD	LOT	Time* (Sec)	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	PROD	LOT	Time* (Sec)	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p* (Tvs.R)**
		0.015															0.015														
		0.030															0.030														
		0.045															0.045														
	1	0.060														1	0.060														
		0.090															0.090														
		0.120															0.120														
		.															.														
		0.015															0.015														
		0.030															0.030														
TEST	2	0.045													REF	2	0.045														
		0.060															0.060														
		0.090															0.090														
		0.120															0.120														
		.															.														
		0.015															0.015														
		0.030															0.030														
	3	0.045														3	0.045														
		0.060															0.060														
		0.090															0.090														
		0.120															0.120														
		.															.														

** Postactuation delay times noted here may need optimization based on nasal spray plume characteristics. Different delay times may be appropriate for pressurized aerosol products. For additional information, see Nasal BA/BE Guidance*

*** Based on combined data of three lots*

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JAN 23 2003

Ipratropium Bromide Solution
0.06% Nasal Spray, 42 μg/spray
ANDA #76-103
Reviewer: Mamata S. Gokhale
v:\firmsam\bausch\ltrs&rev\76103A0902.doc

Bausch & Lomb Pharmaceuticals, Inc.
8500 Hidden River Parkway
Tampa
Florida 33637
Submission Date: September 19, 2002

Review of an Amendment containing In Vitro Performance Data

Background

The firm submitted original ANDA on 1/18/02 for Ipratropium Bromide Nasal Spray, 0.06%. The reference-listed drug (RLD) is Atrovent® Nasal Spray, 0.06% (42 μg/spray, NDA #20-394) manufactured by Boehringer Ingelheim Pharmaceuticals Ltd. The RLD is designed to deliver 165 sprays of 70 μL each (42 μg ipratropium bromide). To demonstrate bioequivalence of the proposed product with the RLD, the firm submitted comparative data to support:

- Q1 and Q2 sameness of the proposed and innovator formulations, and
- Equivalent performance of the test and reference product devices

The comparative performance of the drug delivery devices of the test and reference products was based on the following tests:

1. Unit Dose/Content Uniformity
2. Priming, loss of prime, and tail off
3. Droplet size distribution by at least 2 methods
4. Spray pattern
5. Plume geometry

The DBE found the formulation of the test product acceptable. However the submission was found incomplete due to following deficiencies that were communicated to the firm on 5/30/01.

1. All in vitro tests:

You have used single lots of the test and reference products to determine comparative data for all in vitro testing. The in vitro studies were conducted approximately a year after the issuance of the draft guidance "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action" issued in June 1999. The draft guidance recommends in vitro equivalence based on three lots of the test and reference products, because the proposed method of evaluation takes into consideration the relative

within-lot and lot-to-lot variations of the test and reference products.

Your in vitro performance testing is therefore unacceptable. You are advised to submit data using three lots of the test and reference products for the following in vitro tests:

1. *Unit Dose/Content Uniformity*
2. *Priming, loss of prime, and tail off*
3. *Droplet size distribution by at least two methods*
4. *Spray pattern*
5. *Plume geometry*

2. Droplet size distribution:

With regard to the testing procedure, you have not stated the stage of plume formation for which the D50 and SPAN data were collected. When you repeat this test using three lots of the test and reference products, it should be performed at the beginning, middle and end of product life and at three distances between the orifice and the laser beam. For each spray, please submit D10, D50, D90 and SPAN data for the following three stages of the plume formation based on obscuration (or %transmission) of the laser beam

(1) Plume formation characterized by increase in obscuration
(2) Fully formed plume characterized by a period of relatively stable obscuration
(3) Dissipating plume characterized by decrease in obscuration relative to the stable obscuration

The above data should be accompanied by representative ($\geq$ 20%) graphs of obscurations vs. time (msec). These graphs should also contain plots of D10, D50 and D90 vs. time data. Furthermore, if possible, please submit data regarding the duration of the "fully formed" plume of test and reference products.

Additionally, the Agency recommends the following:

1. Comparability of spray devices:

Please submit technical/engineering drawings of the test and reference pumps.

2. Plume geometry data:

The Agency recommends using only 3 time-delays – e.g. 0.033, 0.066 and 0.100 seconds, instead of the 6 time-delays - 0.0167, 0.0334, 0.0501, 0.0668, 0.0835, 0.1002 seconds used in your Plume Geometry study.

3. Data submission:

Please submit data electronically for the lots of the test and reference products in spread-sheet format as attached herewith. Test/Reference ratios based on geometric means are also requested. Please note that the minimum ANDA batch size should be 5000 bottle. Please indicate the number of bottles in each lot of the test product.

Prior to responding to the deficiencies, the firm consulted the DBE regarding its proposal for analysis of droplet size distribution by laser diffraction and asked for the electronic template for data submission (9/26/01). The DBE found the firm's proposal acceptable and asked the firm to submit single D10, D50, D90 and SPAN values for only the stable region of each spray in a spreadsheet format. The DBE indicated that i) criteria for identifying the initiation and termination of the stable region should be specified in the protocol/SOP and ii) requested ≥ 20% time-history plots, over the entire life of the spray (instrument onset to offset), containing the %obscuration, D10, D50 and D90 data for a given spray on the same plot. Each plot should be labeled to identify the stable region of the plume, distance, product life stage, and the product, batch number and bottle number (12/20/01).

In this amendment, the firm has responded to the deficiencies based on the communications with the DBE.

Firm's response to deficiencies:

Comparability of Spray Devices:

——————— developed and provided to Bausch and Lomb a nasal spray pump exhibiting performance properties comparable to those of the innovator product. Both the pumps are made by the same manufacturer, use the same operating principles and same material of construction. Only difference is in the concentration of the blue colorant used in the gasket, i.e. ——% in the RLD vs —% in the test product. See pages 29-35 of volume 1.5 for details on comparison of spray devices, bill of materials and assembly drawings for the device, actuator and the pump used in the test and reference products (attachment 1).

All in vitro tests

Procedures applicable to all in vitro tests were same as those reported in the original submission. All actuations of the nasal spray products were done using an automated actuator to actuate the nasal sprays in a reproducible manner. The automated actuator is a proprietary unit designed by ——————— for nasal spray actuation. The actuation parameters for this system are described below:

Dose Time: 20 msec. ± 1
Return Time: 50 msec. ± 1
Hold Time: 0.5 sec.
Spray Force: 5.50 ± 0.05 kg

Drug Product lots used in all vitro testing

Product	Lot #	Mfg. Da	Exp. Date	Assay (%)
*Test	306081 (original submission)	6/00	-	100.6
	306082	6/00	N/A	99.7
	306083	6/00	N/A	100.4
Reference	869005A (original submission)	-	6/01	100.6
	157231A	-	7/03	97.5
	157250A	-	7/03	98.6

*All three lots of the test product were filled from the same bulk lot #30608 (see the chemistry review dated 10/19/02).

Statistical Analysis

For all in vitro tests, the firm analyzed data for the test and reference drug products by calculation of mean values and the variability (%cv). ANOVA was used to compare the mean for test product to the mean for reference product at each stage. The 90% confidence intervals for the ratio of true means (true mean of Test over true mean of Reference product) were constructed using Fieller's theorem.

Unit Dose/Content Uniformity:

Testing was performed according to method C-1580 for 10 units each of three reference and three test product lots for all sprays including priming (actuations #1-7), beginning (actuations #8-17), middle (actuations #86-95), and end (actuations #163-172) of use life. The amount actuated per spray was measured by a validated HPLC analysis, Method C-1579 with measurement by weight recorded as supportive data. Both methods were found acceptable in the original submission.

Acceptance Criteria	
Individual Unit Dosage [label claim = 42 µg/spray]	No unit outside 75-125% of label claim and no more than 1 unit out of 10 outside 80-120% of label claim
Mean Dosage Unit	85-115% of label claim
Individual Spray Weight	——— mg/actuation
Mean Spray weight	63.0-77.0 mg/actuation

Results:

The firm provided raw data for the beginning, middle and end actuations for the 10 bottles each of three lots of test and three lots of reference product. The following data are based on reviewer's calculations.

Unit Content Delivered per Spray (μg) (Volume 1.1, pages 95-100 and volume 5.1, pages 40-64)									
		Mean		Variability (%CV)			TEST/REF		ANOVA
Product	Sector	Arith (N=30)	Geo (N=30)	Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	Arith	Geo	p*
Test	BEG	42.57	42.56	0.52-3.11	3.04	2.19	1.03	1.03	0.000
	END	42.81	42.8	0.32-2.04	2.25	1.91	1.03	1.03	0.000
Reference	BEG	41.2	41.2	0.54-1.75	1.46	2.15			
	END	41.63	41.61	0.71-2.42	2.2	3.11			

*Test p = 3.11E-09 and Ref p = 1.22E-07

Unit Weight Delivered per Spray (mg)									
		Mean		Variability (%CV)			TEST/REF		ANOVA
Product	Sector	Arith (N=30)	Geo (N=30)	Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	Arith	Geo	p*
Test	BEG	73.84	73.84	0.36-0.95	0.44	1.02	1.03	1.03	0.000
	END	74.47	74.45	0.32-0.41	0.06	1.75	1.03	1.03	0.000
Reference	BEG	71.55	71.53	0.56-0.9	0.26	2.24			
	END	72.07	72.04	0.48-0.94	0.36	3.15			

*Test p = 1.21E-11 and Ref p = 1.22E-11

Comments on the Unit Dose Data

1) For the test product, geometric mean values at actuations 8 and 172 values are 3% higher than the corresponding reference product values. The test product exhibited slightly higher variability (%CV) than the reference product at the beginning (#8) while the reference product exhibited slightly higher variability (%CV) than the test product at the end (#172) with regard to the unit dose data. The test/ref ratios are within the 90-111% limits, used by DBE for acceptance of *in vitro* performance of solution nasal spray products.

2) The quantity of the drug assayed is based on each single spray. Each bottle is labeled to deliver 165 sprays. The minimum and maximum values for the test product show that the delivered doses fall within 96.6-104.5% of the labeled dose. These values are within the draft guidance recommendations which state that not more than one unit should be outside 80-120% of the label claim, none should be outside 75-125%, and mean values should not be outside 85-115%. The sponsor's

data demonstrated that quantity of drug substance delivered per spray is same for the test and reference products through the product life.

3) Based on the mean values, there was no change in the unit dose determined at the beginning and end sectors. Furthermore, the data did not show a particular trend in changes in variability through the container life.

4) There is a good correlation between the quantity of the drug delivered per spray obtained by weight and that obtained by the HPLC assay.

5) The unit spray content data are acceptable.

Priming, prime retention and tail off characteristics:

The labeling of the test and reference products states: *"Initial pump priming requires seven sprays of the pump. If used regularly as recommended, no further priming is required. If not used for more than 24 hours, the pump will require two sprays, or if not used for more than seven days, the pump will require seven sprays to reprime."*

Priming: The firm has submitted data for sprays #8-10 for 3 bottles each of three lots of the test product and 3 bottles each of three lots of the reference product using the HPLC assay. The firm has also submitted a graphic depiction of priming data demonstrating that by the 7th actuation of all lots, the labeled dose was delivered for the test and reference products (Volume 1.1, pages 95-100 and volume 5.1, pages 40-64).

Prime Retention: The firm has conducted a study to test the ability of the test and reference pump systems to maintain prime after a given time period from last use. After initial testing for priming of all the test and reference lots, the pumps were tested for non-use periods of 1, 7, and 10 days. The firm submitted data on the dose delivered for test and reference products as described below using the validated HPLC assay (volume 5.1, pages 191-205).

Prime Retention Time	No. of units and lots tested		No. of sprays analyzed
	Test	Reference	
After 1 day on non-use	3 lots, 3 bottles/lot	3 lots, 3 bottles/lot	3 sprays after 2 re-priming sprays
After 7 days on non-use	3 lots, 4 bottles/lot	3 lots, 4 bottles/lot	3 sprays after 7 re-pri sprays
After 10 days on non-use	3 lots, 3 bottles/lot	3 lots, 3 bottles/lot	3 sprays after 7 re-pri sprays

Tail off: The firm has submitted data for sprays #173 (corresponding to 165th primed spray) and beyond for 10 bottles each of three lots of the test product and 10 bottles each of three lots of the reference product using HPLC assay. There were

ample therapeutic sprays beyond #165 to allow for periods when the product is not used, and to allow for the cleaning of the actuator and repriming (Volume 1.1, pages 95-100 and volume 5.1, pages 40-64).

Results:

Priming and tail off

Figure 1

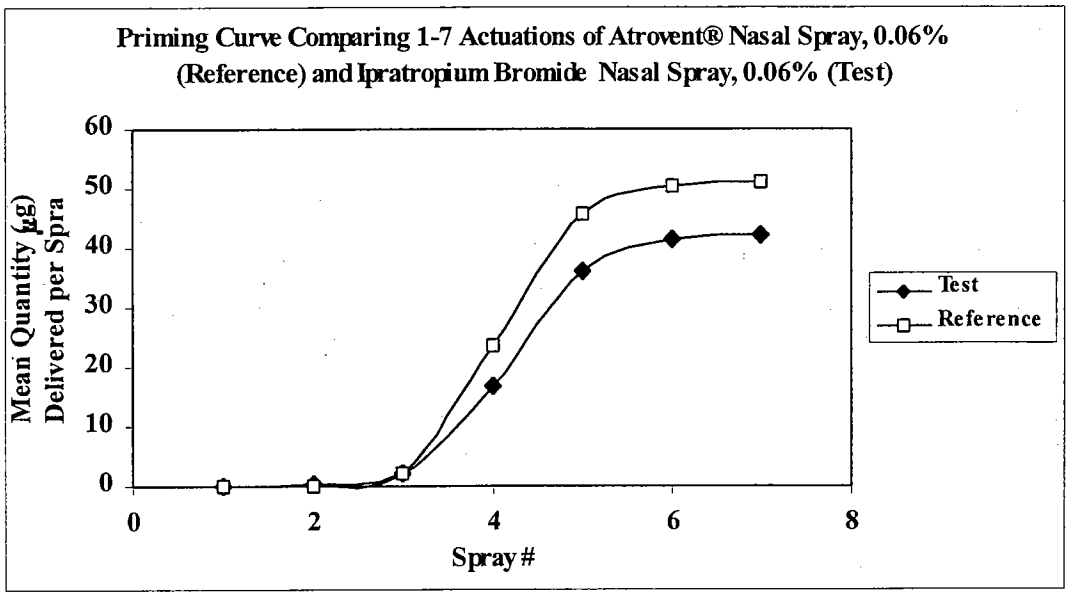
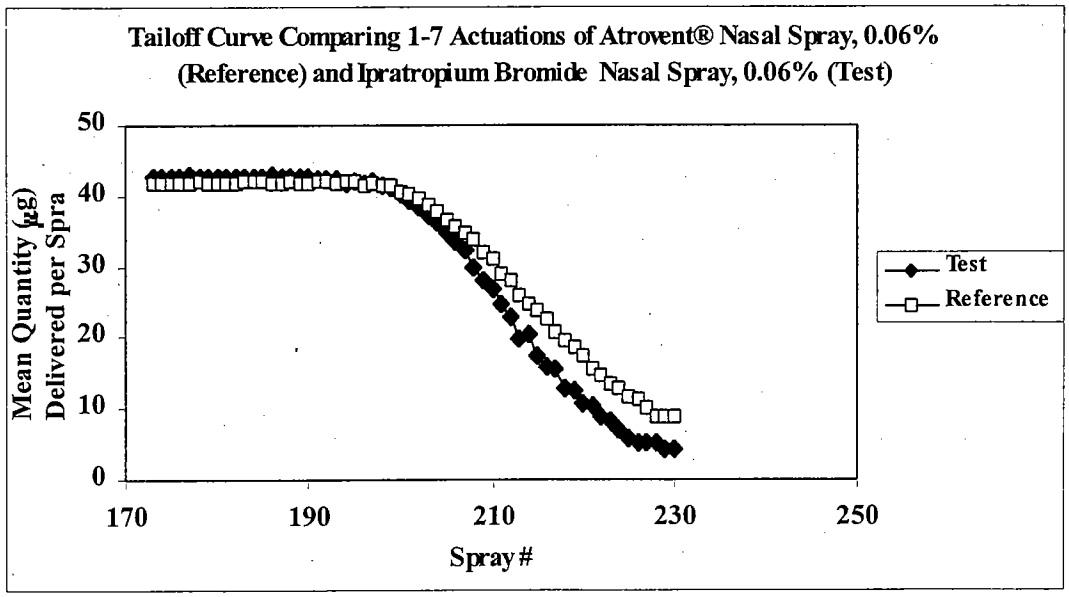


Figure 2



Prime Retention

Period of non use	*Test Mean (%cv)	*Reference Mean (%cv)
0 day (sprays # 8, 9 and 10)	39.91 (1.01)	39.98 (0.29)
	39.98 (1.10)	40.00 (0.19)
	39.67 (1.27)	40.05 (0.19)
1 day (sprays # 13, 14 and 15)	41.34 (2.20)	41.28 (1.77)
	41.03 (2.07)	40.41 (1.36)
	41.34 (1.79)	40.56 (1.01)
7 days (sprays # 18, 19 and 20)	40.97 (2.03)	41.63 (1.15)
	42.22 (2.28)	40.99 (0.76)
	41.77 (1.34)	41.57 (1.23)
10 days (sprays # 18, 19 and 20)	42.10 (0.74)	41.17 (1.70)
	42.37 (0.59)	41.05 (1.88)
	42.28 (0.73)	41.20 (2.14)

*Average of three lots, see summary on pages 210, 213, 218 and 223 of volume 5.1.

Comments on the priming, prime retention and tail off data:

1) Based on the data obtained, the test product is fully primed at the 6th spray as seen in Figure 1.

2) Prime retention study indicates that 98-101% label claim was retained by the test product compared to 96-99% label claim retained by the reference product. These data showed that the test and reference products have similar prime retention characteristics after 1, 7 or 10 days of non use.

3) The tail off profile characterizes decrease in emitted dose following delivery of the labeled number of actuations. It was documented by tabulating the spray weights from spray No. 173 (corresponding to full spray No. 165) to product exhaustion. Data given in Figure 2 indicate that tail off of the test product is no more erratic than that of the reference product.

4) The study demonstrates that like the reference product, the test product meets the provisions of labeling with respect to priming, prime retention and tail off.

Droplet Size Distribution:

Laser Diffraction

Testing was performed on the _____ with one spray per test per distance (duplicate testing per interval). Testing was performed on 10 units each of three lots of the reference and three lots of the test product at beginning, middle and end of use life at 3, 5 and 7 cm distances from the laser beam (sprays #8-9, 86-87 and 163-164 from 3 cm, #10-11, 88-89 and 165-166 from 5 cm and #12-13, 90-91 and 167-168 from 7 cm).

Two instruments were used in conjunction with each other to make the analysis completely automated. The ——————————— mechanically actuated the nasal spray into the ———————————, the laser diffractor that measured the droplet size. The firm states that this test was not blinded because the actuation of spray pumps for both the test and reference products was automated, and all analyses were performed by the instrument. The firm submitted representative (≥ 20%) graphs of obscurations vs. time (msec). For each spray, the firm provided D10, D50, D90 and SPAN data for the following three stages of the plume formation based on obscuration (or %transmission) of the laser beam:

- Plume formation characterized by increase in obscuration.
- Fully formed plume characterized by a period of relatively stable obscuration.
- Dissipating plume characterized by decrease in obscuration relative to the stable obscuration.

Results

Droplet Size Distribution (D50)									
(Volume 5.1, pages 76-105)									
		Mean		Variability (%CV)			T/R ratio		p*
Product	**D50**	Arith (N=30)	Geo (N=30)	Within-lot (N=10)	Between-lot (N=3)	Total (N=30)	Arith	Geo	
	3 cm								
TEST	Beginning	31.14	30.87	2.92-9.05	5.87	14.25	0.88	0.90	0.3067
	Middle	32.43	32.33	3.83-10.37	3.07	8.28	1.01	1.01	0.1749
	End	31.04	31.02	1.95-21.28	1.15	3.41	1.00	1.00	0.0699
REF	Beginning	35.29	34.48	3.83-4.88	14.44	23.58			
	Middle	31.96	31.90	9.31-22.18	0.70	6.28			
	End	30.97	30.89	4.06-25.00	1.65	7.44			
	5 cm								
TEST	Beginning	36.40	36.36	2.38-5.29	1.01	5.01	1.03	1.03	0.0116
	Middle	36.82	36.77	4.34-6.25	4.01	5.40	1.02	1.02	0.4293
	End	36.23	36.20	3.15-5.78	1.48	4.69	1.00	1.00	0.2624
REF	Beginning	35.34	35.30	3.17-4.85	1.01	4.89			
	Middle	36.05	36.03	3.05-4.15	1.25	3.43			
	End	36.08	36.04	3.91-6.59	1.35	4.47			
	7 cm								
TEST	Beginning	43.10	43.03	3.36-7.15	2.34	5.85	0.99	1.00	0.6420
	Middle	42.90	42.84	5.38-6.44	4.09	5.60	1.01	1.01	0.5570
	End	43.05	42.97	4.09-6.76	1.76	6.42	0.99	0.99	0.3152

REF	Beginning	43.59	43.22	3.50-6.12	9.35	15.05
	Middle	42.45	42.41	3.80-6.18	2.81	4.26
	End	43.50	43.42	3.80-19.86	1.84	6.17

Droplet Size Distribution (SPAN)

(Volume 5.1, pages 76-105)

		Mean		Variability (%CV)			T/R ratio		p*
Product	**SPAN**	Arith (N=30)	Geo (N=30)	Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	Arith	Geo	
	3 cm								
TEST	Beginning	2.40	1.58	4.93-16.23	3.28	14.53	0.88	0.89	0.0029
	Middle	1.30	1.29	7.11-11.82	4.70	10.02	0.90	0.91	0.0624
	End	1.25	1.25	4.01-16.26	3.87	6.20	0.91	0.92	0.0182
REF	Beginning	1.65	1.61	24.50-30.56	2.17	22.90			
	Middle	1.45	1.42	18.11-27.73	10.71	20.69			
	End	1.38	1.35	3.58-13.54	6.56	24.00			
	5 cm								
TEST	Beginning	1.17	1.15	6.58-23.94	4.00	24.06	0.98	0.98	0.399
	Middle	1.04	1.04	6.03-17.83	1.07	6.98	0.96	0.96	0.804
	End	1.05	1.05	5.19-31.16	3.11	6.93	0.95	0.96	0.116
REF	Beginning	1.20	1.17	6.12-13.00	7.97	23.08			
	Middle	1.09	1.09	4.30-16.82	3.65	5.54			
	End	1.11	1.09	3.63-31.25	5.60	17.26			
	7 cm								
TEST	Beginning	1.06	1.05	2.91-22.06	5.39	10.87	0.94	0.94	0.739
	Middle	1.09	1.08	5.64-9.76	3.63	14.19	0.99	1.00	0.691
	End	1.14	1.12	7.92-23.53	9.36	16.89	1.07	1.06	0.954
REF	Beginning	1.13	1.12	8.15-40.23	5.35	14.61			
	Middle	1.10	1.08	5.36-5.93	3.55	24.18			
	End	1.06	1.06	9.13-21.48	5.90	9.09			

Comments on Laser Diffraction

1) The ratios of geometric means of test and reference products for D50 at the beginning middle and end sectors at 3, 5 and 7 cm range from 0.90-1.03 which are within the acceptable range. Except for the ratio at the beginning of plume formation at 5 cm, the P values are insignificant for most comparisons.

2) The ratios of geometric means of test and reference products for SPAN at the beginning middle and end sectors at 3, 5 and 7 cm vary from 0.89 to 1.06 range. The

ratio at the beginning of plume formation at 3 cm is below the acceptable range of 0.90-1.11. However the average ratio of geometric means of test and reference at the beginning, middle and end of plume formation at 3 cm is 0.91 which is within the acceptable range. Except for the beginning and end of plume formation at 3 cm, the p values are insignificant for most comparisons.

3) Based on the mean values,

a. The D50 values increased with increase in distance between the actuator and the laser beam but did not change with different product life sectors within each distance.
b. Total variability was generally low at the middle and end sectors for both D50 and SPAN.
c. For the test and reference products, total variability of D50 was generally less than that of the SPAN. For both measures, total variability of the test product was comparable to that of the reference product.
d. Based on the geometric mean data, the Test/Reference ratio for the D50 and SPAN data (except at the beginning sector at 3 cm) are within 0.9-0.11 range used by the DBE for acceptance of *in vitro* performance of solution nasal spray products. However based on analysis of pooled data (beginning, middle and end sectors) all ratios are within the acceptable range of 0.9-1.11. Pooling of data from various sectors is acceptable, because the parameter values do not vary between the sectors.

4) Distribution of droplets in the test product spray is similar to that of the reference product spray.

Droplet Size Distribution:

Cascade Impaction

The ——— cascade impactor selectively segregates particles less than about 10 microns in diameter. Cascade impaction was performed to determine that there is not an excess mass of fines in the test product relative to the RLD. Testing was performed on 10 units each of three lots of the test and three lots of the reference drug product at beginning (sprays #8-17) and end (sprays #163-172) of the product use life. There were 10 actuations per test. Setup of the ——— cascade impactor instrument included

[redacted]

HPLC method. Testing was performed in a blinded manner to hide the identity of test and RLD products from the analyst. For this test, the units were manually actuated (10 actuations per test).

Results

The firm submitted % recovery results obtained by HPLC analysis for each group and the total of all groups using a validated method. The peak area was linear over a range of ——— to ——— The limit of detection was ———. The LOQ was ——— and the %cv was 0.075 (see archival volume 1.2, pages 0665-0690). The groups are described below:

- Group 1 included drug deposited on the throat, ——— and stage 0.
- Group 2 included drug disposition on stage 1 (the stage immediately below the upper stage).
- Group 3 included stages — and the filter.
- Overall total included throat, stages — and filter.

% Recovery (Cascade Impaction) per Spray (Volume 1.1, pages 161-163 and 5.1, pages 235-237)									
		Mean		Variability (%CV)			T/R ratio		p*
Product	**Group 1**	Arith	Geo	Within-Lot	Between-lot	Total	Arith	Geo	
		(N=30)	(N=30)	(N=10)	(N=3)	(N=30)			
TEST	BEG	93.69	93.67	1.65-1.98	0.18	1.91	0.98	0.98	0.002
	END	93.66	93.65	1.57-2.23	0.37	1.83	1.00	1.00	0.484
REF	BEG	95.14	95.1	1.80-2.08	0.27	2.69			
	END	93.99	93.97	1.87-2.27	0.23	2.40			
Product	**Group 2**								
TEST	BEG	0.83	0.81	9.64-26.26	1042	18.65	1.01	1.01	0.902
	END	0.86	0.84	9.40-28.88	1150.2	19.36	1.04	1.05	0.479
REF	BEG	0.83	0.81	11.92-27.07	984	21.41			
	END	0.83	0.81	13.48-30.14	1032.8	22.19			
Product	**Group 3**								
TEST	BEG	1.08	0.7	29.96-148.87	5813	70.22	1.01	NE	0.217
	END	1.78	1.69	8.77-49.96	1224.8	30.89	1.04	1.05	0.212
REF	BEG	1.30	NE	23.88-42.80	747.29	37.38	0.83	NE	
	END	1.67	1.57	10.58-42.52	976.07	29.79	1.07	1.07	

Product	**Total**								
TEST	BEG	95.87	95.85	1.41-2.01	0.36	1.87	0.99	0.99	0.001
	END	96.31	96.3	1.52-2.41	0.46	1.94			0.715
REF	BEG	97.27	97.24	1.38-2.43	0.54	2.54			
	END	96.49	96.46	1.72-2.55	0.43	2.34			

Comments on Cascade Impaction:

1) The amount of drug collected in groups 2 and 3 constitute about 2% of the total drug collected from the cascade impactor apparatus. This fraction represents fine particles (< 10 microns in diameter).

2) The ratios of geometric means of test and reference products for group 1 at the beginning and end of product life, respectively, are 0.98 and 1.00 which are within the acceptable range of 0.90-1.11. The within-lot and total variabilities of the reference product are higher than the test product.

3) The ratios of geometric means of test and reference products for group 2 at the beginning and end of product life, respectively, are 1.01 and 1.05 which are within the acceptable range of 0.90-1.11. The ratio of geometric means of test and reference products for group 3 could not be estimated at the beginning but it was 1.05 at the end of product life, which is within the acceptable range of 0.90-1.11.

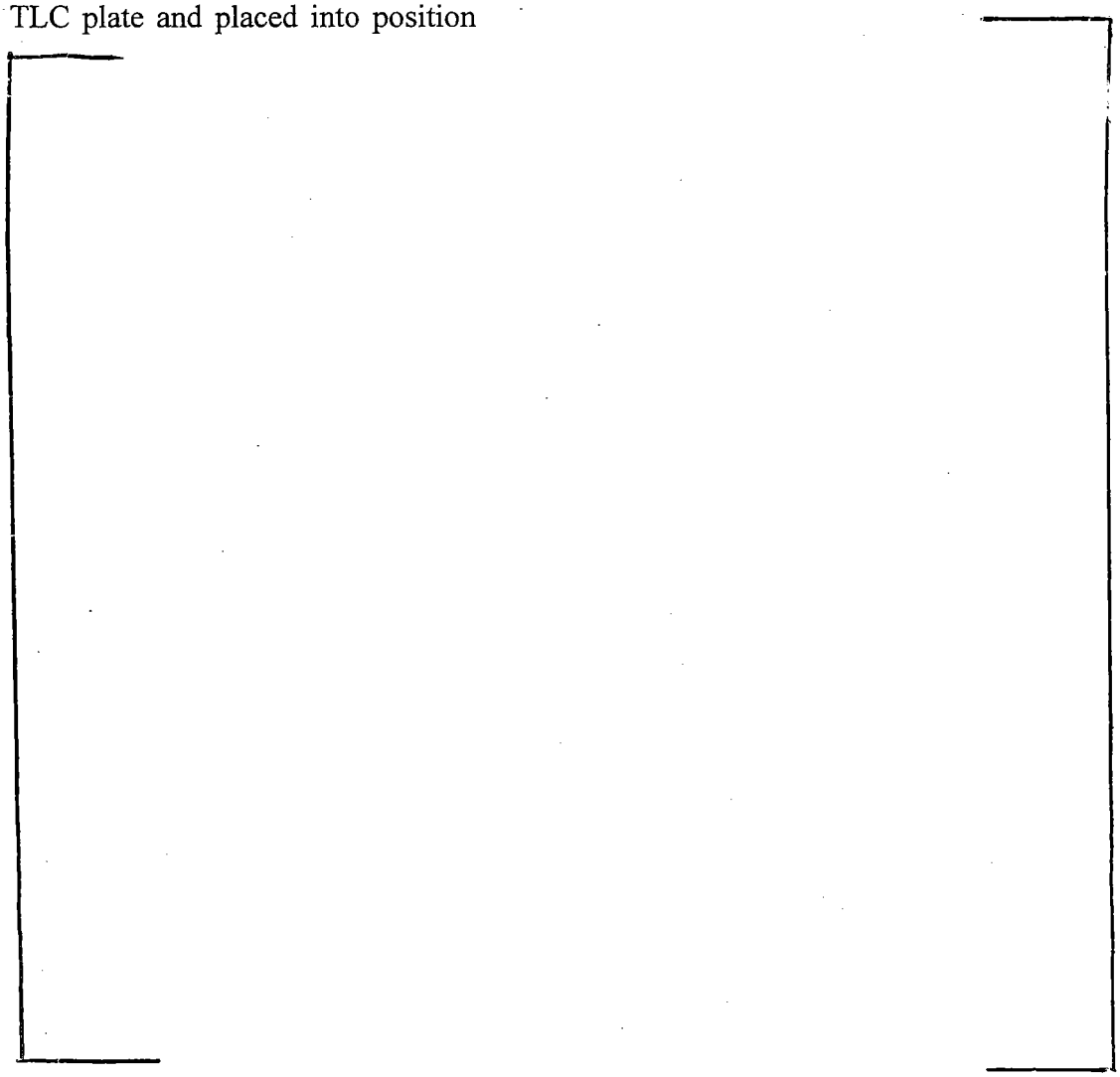
4) The cascade impaction data are acceptable.

Spray pattern:

Spray pattern testing was done on 10 units each of three lots of the test product and three lots of the reference product at 3, 4, and 5 cm distances from nozzle to plate, and tested at beginning (8^{th} actuation) and end (163^{rd} actuation) of the use life. Duplicate testing was conducted for each of the three distances — 1 spray at 3 cm, 1 spray at 4 cm, 1 spray at 5 cm. For visualization of the spray pattern on the plate, the TLC plate ——————————————— was evenly sprayed with ——————— solution (a pH sensitive indicator), turning the plate a pale orange color. The image was read using an UV light at 254 nm, leaving a green pattern wherever the formulation rests on the black background of the plate. Color images were then digitized and analyzed by the ——————— ——————————. This system automatically determines the longest and shortest radii and calculates the corresponding spray angles, the elliptical ratio (longest/ shortest angle), and the ovality ratio (longest/shortest diameter).

The test was not blinded as all units were mechanically actuated with no analyst mechanical intervention on the results. The results are measured by computer.

Operation of [redacted] Once the pattern is detected on a TLC plate and placed into position



The above mentioned method has been used by the firm for another drug product, ANDA 74-830 for Desmopressin Acetate nasal spray approved by the OGD on 1/25/99.

Spray pattern data

(Volume 1.1, pages 188-193 and volume 5.1, pages 155-166)

				Mean		Variability (%CV)		
			Plume	Arith	Geo	Within-Lot	Between-lot	Total
Product	Sector	Distance	Formation	(N=30)	(N=30)	(N=10)	(N=3)	(N=30)
		3	Dmax	6.17	6.16	6.55-8.55	3.16	7.82
		3	Dmin	5.42	5.40	4.52-8.55	5.35	8.54
		3	Ovality Ratio	1.14	1.14	2.22-3.23	2.36	3.42

		4	Dmax	7.58	7.54	5.19-12.01	3.63	10.43
	BEG	4	Dmin	6.46	6.42	6.49-11.76	6.8	11.35
		4	Ovality Ratio	1.18	1.17	2.35-4.63	3.83	4.61
		5	Dmax	8.11	8.06	7.04-13.75	3.70	10.94
		5	Dmin	6.69	6.63	8.01-15.30	8.06	12.51
TEST		5	Ovality Ratio	1.22	1.22	1.89-6.19	3.46	5.13
		3	Dmax	6.19	6.17	5.23-9.33	7.00	8.99
		3	Dmin	5.34	5.32	5.90-10.09	3.87	8.31
		3	Ovality Ratio	1.16	1.16	2.78-3.18	4.21	4.51
		4	Dmax	7.30	7.27	5.23-10.84	3.86	8.67
	END	4	Dmin	6.32	6.30	4.76-11.25	3.28	8.80
		4	Ovality Ratio	1.16	1.15	2.94-3.07	3.44	4.07
		5	Dmax	8.22	8.16	9.87-14.14	4.52	11.65
		5	Dmin	6.91	6.87	9.67-12.57	5.12	11.21
		5	Ovality Ratio	1.19	1.19	3.71-3.77	4.18	4.91
		3	Dmax	6.30	6.27	7.20-9.75	5.50	9.46
		3	Dmin	5.52	5.51	6.32-8.15	5.02	8.28
		3	Ovality Ratio	1.14	1.14	3.37-7.57	2.17	5.41
		4	Dmax	7.46	7.41	9.05-11.80	6.40	11.30
	BEG	4	Dmin	6.29	6.26	5.60-11.56	5.57	9.18
		4	Ovality Ratio	1.19	1.18	4.89-9.06	1.10	6.54
		5	Dmax	8.34	8.24	11.23-14.79	13.03	16.79
		5	Dmin	6.91	6.85	8.91-12.46	11.62	14.13
Reference		5	Ovality Ratio	1.21	1.2	5.43-7.89	3.34	7.08
		3	Dmax	6.08	6.04	7.56-10.05	8.19	11.37
		3	Dmin	5.23	5.21	7.09-7.66	6.91	9.16
		3	Ovality Ratio	1.16	1.16	3.57-6.88	3.93	6.28
		4	Dmax	7.21	7.16	8.87-12.52	7.81	12.82
	END	4	Dmin	6.17	6.13	6.35-10.48	7.42	10.50
		4	Ovality Ratio	1.17	1.17	4.36-7.39	1.47	5.53
		5	Dmax	8.12	8.05	10.53-12.71	9.08	13.49
		5	Dmin	6.82	6.78	7.95-11.74	8.00	11.36
		5	Ovality Ratio	1.19	1.19	5.34-10.42	3.92	7.79

Spray pattern Data Continued

		TEST/REF Ratio		
Dmax		Arith	Geo	p
3 cm	Beg	0.98	0.98	0.398
	End	1.02	1.02	0.406
4 cm	Beg	1.02	1.02	0.567
	End	1.01	1.02	0.657
5 cm	Beg	0.97	0.98	0.413
	End	1.01	1.01	0.694
Dmin				
3 cm	Beg	0.98	0.98	0.344

	End	1.02	1.02	0.286
4 cm	Beg	1.03	1.03	0.297
	End	1.03	1.03	0.248
5 cm	Beg	0.97	0.97	0.251
	End	1.01	1.01	0.591
Ovality Ratio				
3 cm	Beg	1.00	1.00	0.980
	End	1.00	1.00	0.793
4 cm	Beg	0.99	0.99	0.526
	End	0.99	0.99	0.401
5 cm	Beg	1.01	1.01	0.581
	End	1.00	1.00	0.961

Comments on Spray pattern

1) The spray patterns submitted by the firm are distinguishable from the background and can be clearly visualized for Dmin and Dmax. Spray patterns are circular, oval or sometimes spoked in shape and are more intense at shorter distance, i.e. 3 cm.

2) The ratios of geometric means of the test and reference products vary from 0.98-1.02 for Dmax, 0.98-1.03 for Dmin and 0.99-1.00 for ovality ratio at 3, 4 and 5 cm. All ratios are within acceptable range of 0.90-1.11.

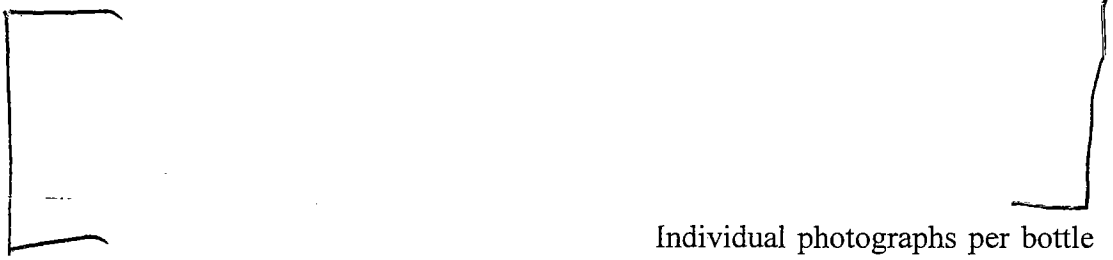
3) For Dmin, Dmax and ovality ratio, total variability of the reference product is higher than the test product at the beginning and end of product life at 3, 4 and 5 cm.

Plume Geometry:

Images of plumes for 10 units each of three lots of the test product and three lots of the reference products were captured photographically at three points within the life of the spray representing the plume at early formation, at intermediate time point and as it began to dissipate. As per the DBE recommendations, three time delays (0.0334, 0.0668 and 0.1002 seconds) were used for plume measurement.

Testing was performed in a blinded manner to hide the identity of test and reference products from the analyst. The units were actuated 7 times to assure prime with the 8th spray being the test. Testing was conducted according to Nasal Instrument Procedure NIP-2000-006 (Section 15, Vol. 1.3, pp.1058-1062). Each plume was sprayed in an upright, stationary position. As it was being filmed, the spray evolved and dissipated in front of a grid calibrated in inches. The room in which testing was performed was ventilation free and sound proof to eliminate any currents or vibration of droplets. There was no exhaust hood above the plume.

The plume (spray cone) angle was measured using [redacted]. The program had a built-in function to allow the analyst to



Individual photographs per bottle are provided in volumes 1.13 and 1.14 and C 5.49-5.54.

Plume geometry (Height, Width and Angle) (Volume 5.1, pages 252-256)									
	Height	Mean		Variability (%CV)			T/R ratio		P*
Product		Arith (N=30)	Geo (N=30)	Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	Arith	Geo	
	0 Degree View								
TEST	0.0334	15.28	15.15	6.97-7.67	5.33	13.98	0.99	0.99	0.145
	0.0668	24.25	24.2	7.76-11.79	1.35	6.36	1.00	1.00	0.088
	0.1002	31.63	31.53	3.84-18.71	1.55	7.91	1.05	1.06	0.307
REF	0.0334	15.41	15.32	6.59-12.66	0.87	11.35			
	0.0668	24.17	24.1	10.07-11.69	2.65	7.46			
	0.1002	30.02	29.84	4.54-12.62	3.20	10.84			
	90 Degree View								
TEST	0.0334	17.87	17.81	5.80-8.09	2.30	7.98	0.94	0.94	0.413
	0.0668	24.76	24.7	7.21-10.02	2.07	7.32	0.92	0.92	0.560
	0.1002	32.41	32.33	5.24-8.60	0.79	6.99	0.98	0.99	4.002E-08
REF	0.0334	19.03	18.85	8.97-18.65	7.50	14.57			
	0.0668	26.92	26.74	7.36-10.92	9.49	11.68			
	0.1002	32.94	32.79	6.62-12.17	6.05	9.53			
	Width								
	0 Degree View								
TEST	0.0334	13.57	13.34	7.99-15.36	9.78	19.34	1.06	1.07	0.266
	0.0668	18.23	18.05	10.80-20.38	6.62	14.64	1.14	1.15	0.006
	0.1002	19.88	19.74	14.01-17.40	6.33	12.16	1.12	1.13	0.005
REF	0.0334	12.79	12.49	12.88-16.55	7.66	21.59			
	0.0668	16.06	15.72	21.18-24.55	6.36	20.13			
	0.1002	17.75	17.44	20.03-22.88	6.01	18.46			
	90 Degree View								

TEST	0.0334	15.34	15.08	9.10-17.71	11.86	18.27	1.06	1.05	0.108
	0.0668	19.45	19.33	7.82-12.15	6.62	11.2	1.03	1.03	0.005
	0.1002	21.13	21.02	9.04-18.01	6.63	10.09	1.02	1.02	0.133
REF	0.0334	14.53	14.37	11.90-15.28	4.37	15.00			
	0.0668	18.91	18.71	14.27-15.82	1.42	14.31			
	0.1002	20.80	20.61	14.19-15.42	2.74	13.28			
	Angle								
	0 Degree View								
TEST	0.0334	87.67	87.51	4.43-5.40	2.59	6.01	1.09	1.11	0.244
	0.0668	90.61	90.51	3.61-5.36	1.22	4.61	1.11	1.13	0.025
	0.1002	89.84	89.71	5.47-7.60	0.68	5.42	1.10	1.11	0.121
REF	0.0334	80.32	79.05	8.97-14.17	10.38	17.23			
	0.0668	81.70	80.41	12.04-16.77	9.05	17.06			
	0.1002	81.72	80.85	16.76-19.86	8.98	14.25			
	90 Degree View								
TEST	0.0334	79.40	79.09	7.77-10.51	4.26	8.75	1.07	1.08	0.994
	0.0668	84.25	84.07	2.57-6.18	2.25	6.52	1.09	1.11	0.010
	0.1002	84.79	84.62	6.70-7.93	1.37	6.23	1.09	1.10	2.385E-06
REF	0.0334	73.92	73.03	10.86-15.05	6.30	15.53			
	0.0668	77.08	75.99	13.53-15.85	9.36	16.47			
	0.1002	77.97	76.98	15.22-18.58	9.66	15.71			

Plume geometry (Fully formed plume at 0 Degree and 90 Degree Views Combined)

(Reviewer's analysis)

	Angle	Mean		T/R ratio	
Product	**0 degree and 90 degree combined**	Arith (N=60)	Geo (N=60)	Arith	Geo
TEST	0.0668	84.30	84.07	1.06	**1.07**
REF	0.0668	79.50	78.34		
	Width	Mean		T/R ratio	
Product	**0 degree and 90 degree combined**	Arith (N=60)	Geo (N=60)	Arith	Geo
TEST	0.0668	19.50	19.33	1.03	**1.03**
REF	0.0668	18.90	18.71		

Comments on Plume Geometry Data

1) Plume measurements at three time delays of 0.0334, 0.0668 and 0.1002 seconds adequately represent three stages of plume life, i.e. initiation, full formation and dissipation.

2) The ratios of geometric means of test and reference products for plume height varied from 0.99-1.06 at the 0^0 view and from 0.92-0.99 at the 90^0 view. The differences between plume height of test and reference products were statistically not significant at initiation, full formation or dissipation stages.

3) The ratios of geometric means of test and reference products for plume width varied from 1.07-1.15 at the 0^0 view and from 1.02-1.05 at the 90^0 view. The differences between plume widths of test and reference products were statistically significant at full formation and dissipation for the 0^0 view and at full formation for the 90^0 view.

4) The ratios of geometric means of test and reference products for plume angle varied from 1.11 to 1.13 at the 0^0 view and from 1.08-1.11 at the 90^0 view. The differences between plume angles of test and reference products were statistically significant at full formation for the 0^0 and 90^0 views.

5) Based on the above data, the geometric mean ratios of test and reference products for plume height are within the acceptable range of 0.90-1.11. However the geometric mean ratios of test and reference products for plume width and angle for the 0 degree view are outside the range of 0.90-1.11 used by the DBE as an acceptance criteria for the solution nasal spray drug products. The drug product actuator does not have a specified index mark to help its positioning for a given 0 degree or 90 degree view. Therefore, the Agency is currently revising its recommendation to propose only a single view data. In view of this proposal from the OINDP in vitro working group, the data for the 0 degree and the 90 degree views were combined. Based on the analysis of the combined data the geometric mean ratios of test and reference products for plume angle and width are within the acceptable range of 0.90-1.11.

6) The plume geometry data are acceptable.

Overall Comments

1) The firm has previously submitted information indicating that composition of the test product formulation is qualitatively and quantitatively same as that of the reference listed drug.

2) The firm has demonstrated that the in vitro performance of the test product is similar to that of the reference product, based on tests for i) Unit spray content, ii) priming, prime retention and tail off, iii) droplet size distribution by laser diffraction and cascade impaction, iv) Spray pattern, and v) Plume geometry.

Recommendations

1) The in vitro performance testing conducted by Bausch and Lomb on its Ipratropium Bromide Nasal Spray, 0.06%, Lots #306081, 306082 and 306083 comparing them with the reference product, Atrovent® Nasal Spray, 0.06%, Lots #869005A, 157231A and 157250A has been found acceptable by the Division of Bioequivalence.

2) The formulation of Bausch and Lomb's Ipratropium Bromide Nasal Spray, 0.06% is qualitatively and quantitatively (Q1 and Q2) same as the RLD, Atrovent® Nasal Spray, 0.06%, manufactured by Boehringer Ingelheim Pharmaceuticals Ltd.

The firm should be informed of the recommendations.

Mamata S. Gokhale, Ph.D. Mamata Gokhale 1/16/03
Division of Bioequivalence

RD INITIALED GJP Singh, Ph.D.
FT INITIALED GJP Singh, Ph.D. GJP Singh Date 1-21-03

Concur: Dale P. Conner Date 1/23/03
Dale P. Conner, Pharm.D. Director
Division of Bioequivalence

cc: ANDA# 76-103 (original, duplicate), Davit, HFD-658, Gokhale, HFD-658, Drug File, Division File

APPEARS THIS WAY ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA: 76-103 APPLICANT: Bausch & Lomb Pharmaceuticals, Inc.

DRUG PRODUCT: Ipratropium Bromide Nasal Spray 0.06%

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA # 76-103
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer: M. Gokhale
HFD-658/ TL: GJP. Singh

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Printed in final on 1/16/2003

Endorsements: (Final with Dates)
HFD-658/ M. Gokhale 1/16/03
HFD-650/ GJP Singh GJPS 1-21-03
HFD-650/ D. Conner 1/23/03
HFD-617/ S. Mazzella

BIOEQUIVALENCY – Complete Submission Date: 9/19/2002

Amendment (STA) Strength: 0.06%
Outcome: AC

Outcome Decisions:

AC – Acceptable

WinBio Comments:

Study amendment is acceptable

Redacted 7 page(s)

of trade secret and/or

confidential commercial

information from

BIOEQUIVALENCE REVIEW OF 9/19/2002 SUBMISSON
[ATTACHMENT]

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-103 SPONSOR : Bausch & Lomb Pharmaceuticals, Inc.
DRUG AND DOSAGE FORM : Ipratropium Bromide Nasal Spray

STRENGTH(S) : 0.06%

TYPES OF STUDIES : SD SDF MULT OTHER

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : BLP Hidden River Facility, Tampa Florida

STUDY SUMMARY : The in vitro studies on Bausch & Lomb's Ipratropium Bromide Nasal Spray, 0.06% and Atrovent® Nasal Spray 0.06% were found to be acceptable.

DISSOLUTION : N/A

DSI INSPECTION STATUS

Inspection needed: ~~Yes~~ NO	Inspection status:	Inspection results:
First Generic __No__ New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : MAMATA S. GOKHALE, Ph.D. BRANCH : III

INITIAL : MSG DATE : 1/16/03

TEAM LEADER : GJP. SINGH, Ph.D. BRANCH : III

INITIAL : GJPSingh DATE : 1-21-03

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm.D.

INITIAL : DPC DATE : 1/23/03

76-103 5.1

Ipratropium Bromide Solution
0.06% Nasal Spray, 42 µg/spray
ANDA #76-103
Reviewer: Mamata S. Gokhale
v:\firmsam\bausch\ltrs&rev\76103A0902.doc

Bausch & Lomb Pharmaceuticals, Inc.
8500 Hidden River Parkway
Tampa
Florida 33637
Submission Dates: ~~1/18/02~~ and 9/19/02

Addendum to the Review of an Amendment containing In Vitro Data

The firm submitted original ANDA on 1/18/02 and the amendment on 9/19/02 for Ipratropium Bromide Nasal Spray, 0.06%. The reference-listed drug (RLD) is Atrovent® Nasal Spray, 0.06% (42 µg/spray, NDA #20-394) manufactured by Boehringer Ingelheim Pharmaceuticals Ltd. The firm submitted formulation and in vitro performance data comparing the test product with the RLD. In the unit dose/content uniformity and cascade impaction testing, amount of ipratropium bromide actuated per spray was measured by a validated HPLC analysis, Method C-1579. These data were found acceptable. However the DBE has not yet informed the firm in writing.

It has been discovered that the firm used a calibration curve containing only one concentration of the standard with a fit linear through zero in order to calculate the amount of ipratropium bromide actuated per spray. A calibration curve should usually consist of several non-zero concentrations covering the expected range of analyte in the samples. Therefore, the firm should explain and justify the use of only one concentration of standard in the calibration curve in the sample analysis using HPLC Method C-1579.

Mamata S. Gokhale, Ph.D. Mamata Gokhale 2/14/03
Division of Bioequivalence

RD INITIALED GJP Singh, Ph.D.
FT INITIALED GJP Singh, Ph.D. GJP Singh Date 2-14-03

Concur: Barbara Mayer Davit Date 3/11/03
for Dale P. Conner, Pharm.D. Director
Division of Bioequivalence

cc: ANDA# 76-103 (original, duplicate), Gokhale, HFD-658, Drug File, Division File

Wght R

RS

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA: 76-103 APPLICANT: Bausch & Lomb Pharmaceuticals, Inc.

DRUG PRODUCT: Ipratropium Bromide Nasal Spray 0.06%

The Division of Bioequivalence has noted the following deficiency:

To calculate the amount of ipratropium bromide actuated per spray by HPLC, a calibration curve containing only one concentration of standard and a fit type of linear through zero was used. A calibration curve should usually consist of six to eight non-zero concentrations covering the expected range of analyte in the samples. Please explain and justify the use of only one concentration of standard.

Sincerely yours,

for Barbara Myles Conner

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA # 76-103
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer: M. Gokhale
HFD-658/ TL: GJP. Singh

V:\FIRMSAM\BAUSCH\LTRS&REV\76103A0902.DOC
Printed in final on 2/14/2003

Endorsements: (Final with Dates)
HFD-658/ M. Gokhale MGK 2/14/03
HFD-650/ GJP Singh GJPS 2-14-03
for HFD-650/ D. Conner BNC 3/1/03
HFD-617/ S. Mazzella

BIOEQUIVALENCY – Incomplete

Submission Dates: ~~1/18/02~~ & 9/19/2002

Amendment (STA)

Strength: 0.06%
Outcome: IC

Outcome Decisions:

IC – Incomplete

WinBio Comments:

Incomplete

Ipratropium Bromide Solution Nasal Spray
0.06% (42 µg/spray)
ANDA # 76-103
File #V:\FIRMSAM\BAUSCH\LTRS&REV\76103AD314.doc

Bausch & Lomb Pharmaceuticals, Inc.
8500 Hidden River Parkway
Tampa
Florida 33637
Submission Dates: 1/18/02 and 9/19/02

An Addendum to the Bioequivalency Review

The review of the Bausch and Lomb's ipratropium bromide nasal spray application (76-103 for the 0.06% solution) has identified the following deficiency:

To calculate the amount of ipratropium bromide actuated per spray by HPLC, a calibration curve containing only one concentration of standard and a fit type of linear through zero was used. A calibration curve should usually consist of six to eight non-zero concentrations covering the expected range of analyte in the samples. Please explain and justify the use of only one concentration of standard.

A review of the relevant information revealed that the firm used a validated method with documented linearity in the range of [redacted]. The signal to noise ratio at the lowest concentration (0.05 mcg/mL) was 10. Therefore the assay used by the firm was validated for a wide range of concentration below and above the drug concentration per spray. The same assay was used for determination of concentrations in the tests for the Unit spray content and the cascade impaction analysis.

Based on discussion with the chemistry team leader (Mike Smela) the single calibration standards are routinely used in such chemical analyses based on documented linearity over the range of assayed concentrations. The DBE therefore finds the method acceptable.

Gur Jai Pal Singh
Team Leader
Division of Bioequivalence

Gurjaipal Singh 3-14-03

Concur: Mike Smela M Smela Date: 3/14/03
Team Leader
Division of Chemistry I

Concur: for Dale Conner Barbara M Davis Date: 3/14/03
Director
Division of Bioequivalence

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-103

ADMINISTRATIVE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-103 Applicant **Bausch & Lomb Pharmaceuticals, Inc.**
Drug **Ipratropium Bromide Solution (Nasal Spray), 0.06%**

PROVAL X **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER:

	DRAFT Package	**FINAL Package**
1. Project Manager, Team PETER CHEN Review Support Br Z	Date 2/5/03 Initials PC	Date 2/6/03 Initials PC

Application Summary:

Original Rec'd date 1/18/01
Date Acceptable for Filing 1/18/01
Patent Certification (type) II
Date Patent/Exclus.expires N.A.
Citizens' Petition/Legal Case Yes ☐ No X
(If YES, attach email from PM to CP coord)
First Generic Yes X No ☐
(If YES, Pediatric Exclusivity Tracking System (PETS)
RLD = ATROVENT
Date checked 2/5/03 NDA# 20-394
Nothing Submitted X
Written request issued ☐
Study Submitted ☐
Previously reviewed and tentatively approved ☐ Date
Previously reviewed and CGMP def./N/A Minor issued ☐ Date
Comments:
METHODS VALIDATION BEING CONDUCTED UNDER RELATED ANDA 76-025 (0.03%)

EER Status Pending ☐ Acceptable X OAI ☐
Date of EER Status 12/31/01
Date of Office Bio Review 1/23/03
Date of Labeling Approv. Sum 5/22/02
Date of Sterility Assur. App. N.A.
Methods Val. Samples Pending Yes ☐ No ☐
Commitment Rcd. from Firm Yes X No
Modified-release dosage form: Yes ☐ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐

2. Gregg Davis **PPIV ANDAs Only** Date 3/25/03 Initials
Supv., Reg. Support Branch Date 3/25/03 Initials for

Contains GDEA certification: Yes X No ☐
(required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes X No ☐ #II
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☐ N/A No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Has case been settled: N/A Yes ☐ No ☐
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength:
Comments: There are no unexpired patents listed in the Orange Book for this drug product. Exclusivity I-327 has been addressed by the applicant - this indication will not be included in the labeling until the exclusivity expires.

Determ. of Involvement? Yes ☐ No X
Pediatric Exclusivity System
Date Checked 3/25/03 (X)
Nothing Submitted
Written request issued ☐
Study Submitted ☐
RLD-Atrovent Nasal Spray 0.06% (0.042 mg/s
Boehringer Ingelheim Pharmaceuticals Inc. NDA 20-394
Yes ☐ No X

3. Div. Dir./Deputy Dir. Date 3/18/03
Chemistry Div. I ~~or II~~ Initials
Comments:

The CMC section is satisfactory.

REVIEWER: **FINAL ACTION**

4. Frank Holcombe
Assoc. Dir. For Chemistry
Date _____
Initials _____
Comments: (First generic drug review)
N/A Refer to Dey L.P.'s ANDA 75-552 for this drug product.

5. Peter Rickman
~~Acting~~ Director, DLPS
Date 3/25/03
Initials [illegible]
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Comments: Acceptable, EES dated 12/31/01 Verified 3/25/03 No O.A.I. alerts noted. Bioequivalence studies (in vitro including unit dose, priming, droplet size distribution, spray pattern, cascade impaction, plume geometry) found acceptable 1/21/03, 3/4/03. Formulation is Q+S" to the RLD. Office level bio endorsed 1/23/03. DSI inspection was not requested.

5. Robert L. West
~~Acting~~ Deputy Director, OGD
FPL found acceptable 5/21/02. F-327 exclusivity providing for use of drug product for "seasonal allergic rhinitis" has been "carved out" of the labeling. Use for relief of nasal congestion associated with the common cold remains in the labeling. CMC found acceptable OR 10/9/02. Methods validation is pending under "sister" NDA 76-025 (0.03%). Standard methods validation commitment has been received (original submission).
Date 3/28/2003
Initials Robert West
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Comments:
Upon completion of the first generic CMC audit for a related application, ANDA 75-552, this application is recommended for approval. The F-327 exclusivity has been "carved-out" of the package insert.

6. Gary Buehler
Director, OGD
Date 3/31/03
Initials GB
Comments:

First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

7. Project Manager, Team Peter Chen
Review Support Branch
Date 3/31/03
Initials PC

3/31/03 Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
10:41A Time notified of approval by phone 10:41A Time approval letter faxed

FDA Notification:
3/31/03 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
3/31/03 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-103

CORRESPONDENCE

Pharmaceuticals, Inc. 8500 Hidden River Parkway Tampa FL 33637 813 975 7700 Fax 813 975 7770

NDA for filing
S. Middleton 2/9/01

BAUSCH & LOMB

January 17, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Concur. 14-FEB-2001
Gregory E. Davis

Re: Ipratropium Bromide Nasal Spray, 0.06% ANDA Submission

Dear Sir or Madam:

In accordance with the provisions set forth in 21 CFR 314.94, we are submitting this abbreviated new drug application, in duplicate, for Ipratropium Bromide Nasal Spray, 0.06%. This application consists of 3 volumes of chemistry information, including a summary of the bioequivalence data, and 13 additional volumes of supporting bioequivalence data (a total of 16 volumes).

An analytical methods validation package, which includes 2 additional copies of non-compendial assay procedures and the corresponding validation studies, is provided under separate cover. We will commit to resolve any issues identified in the methods validation process after approval.

Changes which influence the manufacture of Ipratropium Bromide Nasal Spray, 0.06% will be reported to the Agency as established in 21 CFR 314.70.

In accordance with 21 CFR 314.50, we certify that a true copy of the information contained in this application has been forwarded to FDA's Orlando District Office.

If you have any questions regarding this correspondence, please contact me at the above address, by telephone at (813) 975-7775 or fax (813) 975-7757.

Sincerely,

J.B. Hawk

Joseph B. Hawkins
Manager
Regulatory Affairs

Enclosures

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN 18 2001
OGD

ANDA 76-103

Bausch & Lomb Pharmaceuticals, Inc.
Attention: Joseph Hawkins
8500 Hidden River Parkway
Tampa, FL 33637

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Ipratropium Bromide Nasal Solution, 0.06%

DATE OF APPLICATION: January 17, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: January 18, 2001

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Michelle Dillahunt
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-103
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement: HFD-615/GDavis, Chief, RSB Davis 14-FEB-2001 date
HFD-615/SMiddletons, CSO Middleton date 2/12/01
WORD FILE V:\FIRMSAM\BAUSCH\LTRS&REV\76103.ACK
F/T/ EEH 02/12/01
ANDA Acknowledgment Letter!

APPEARS THIS WAY
ON ORIGINAL

Pharmaceuticals, Inc. 8500 Hidden River Parkway Tampa FL 33637 813 975 7700 Fax 813 975 7770

BAUSCH & LOMB

February 14, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: ANDA 76-103, Ipratropium Bromide Nasal Spray, 0.06%
Electronic Files for January 17, 2001 ANDA Submission

Dear Sir or Madam:

The purpose of this correspondence is to provide electronic files for bioequivalence data included in the abbreviated new drug application for Ipratropium Bromide Nasal Spray, 0.06%, submitted to the Agency January 17, 2001. These files were inadvertently omitted from the original submission. Also enclosed is companion document that was created as part of an optional electronic submission we had originally planned for this application. Due to resource issues we were not able to prepare the ESD file but the companion document file may be useful to the Agency. The information in the companion document is identical to the corresponding documents in the paper application.

In accordance with 21 CFR 314.50, we certify that a true copy of the information contained in this application has been forwarded to FDA's Orlando District Office.

If you have any questions regarding this correspondence, please contact me at the above address, by telephone at (813) 975-7700 ext. 7102 or fax (813) 975-7757.

Sincerely,

Joseph B. Hawkins
Manager
Regulatory Affairs

Enclosures

8500 Hidden River Parkway
Tampa FL 33637

813 975 7700
Fax 813 975 7757

B2.1

BAUSCH & LOMB

May 7, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NEW DOCUMENTS
NC

Re: ANDA 76-103, Ipratropium Bromide Nasal Spray, 0.06% Amendment – Alternate Test Laboratory

Dear Sir or Madam:

This correspondence is provided to notify the Agency that we will be using an alternate laboratory for testing of the drug product described in the above referenced ANDA.

Bausch & Lomb is adding our laboratory in Rochester, New York as an alternate test site for drug product. The laboratory will be used for chemical and microbiological testing of drug product samples, including the remaining exhibit batch stability samples for the above referenced ANDA. Testing described in the pre-marketed stability protocol may be performed at the following facility, from this date forward:

Bausch & Lomb, Incorporated
1400 N. Goodman Street
Rochester, NY 14603

A letter certifying compliance of this laboratory with current Good Manufacturing Practices is enclosed. This change affects pre-marketed batches only at test stations from this date forward. All stability testing to date, including data previously submitted to the Agency, was performed at the Bausch & Lomb facility in Tampa, Florida.

If you have any questions regarding this correspondence, please contact me at the above address or by telephone at (813) 975-7775.

Sincerely,

Joseph B. Hawkins
Manager,
Regulatory Affairs

enclosure

BIOEQUIVALENCY AMENDMENT

ANDA 76-103

MAY 30 2001

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Bausch & Lomb Pharmaceuticals, Inc.

ATTN: Joseph Hawkins

TEL: 813-975-7700 ext 7102

FAX: 813-975-7757

PROJECT MANAGER: 301-827-5847

FROM: Steven Mazzella

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on January 17, 2001, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ipratropium Bromide Nasal Spray, 0.06%.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

MAY 30 2001

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA:76-103 APPLICANT: Bausch & Lomb Pharmaceuticals, Inc.

DRUG PRODUCT: Ipratropium Bromide Nasal Spray 0.06%

The Division of Bioequivalence has completed its review of your application acknowledged on the cover sheet. The following deficiencies have been identified:

1. All in vitro tests:

You have used single lots of the test and reference products to determine comparative data for all in vitro testing. The in vitro studies were conducted approximately a year after the issuance of the draft guidance *"Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action"* issued in June 1999. The draft guidance recommends in vitro equivalence based on three lots of the test and reference products, because the proposed method of evaluation takes into consideration the relative within-lot and lot-to-lot variations of the test and reference products.

Your in vitro performance testing is therefore unacceptable. You are advised to submit data using three lots of the test and reference products for the following in vitro tests:

1. Unit Dose/Content Uniformity
2. Priming, loss of prime, and tail off
3. Droplet size distribution by at least two methods
4. Spray pattern
5. Plume geometry

2. Droplet size distribution:

With regard to the testing procedure, you have not stated the stage of plume formation for which the D50 and SPAN data were collected. When you repeat this test using three lots of the test and reference products, it should be performed at the beginning, middle and end of product life and at three distances between the orifice and the laser beam. For each spray, please submit D10, D50, D90 and SPAN data for the following three stages of the plume formation based on obscuration (or %transmission) of the laser beam

(1) Plume formation characterized by increase in obscuration.
(2) Fully formed plume characterized by a period of relatively stable obscuration.
(3) Dissipating plume characterized by decrease in obscuration relative to the stable obscuration.

The above data should be accompanied by representative (≥ 20%) graphs of obscurations vs. time (msec). These graphs should also contain plots of D10, D50 and D90 vs. time data. Furthermore, if possible, please submit data regarding the duration of the "fully formed" plume of test and reference products.

Additionally, the Agency recommends the following:

1. **Comparability of spray devices:**
   Please submit technical/engineering drawings of the test and reference pumps.

2. **Plume geometry data:**
   The Agency recommends using only 3 time-delays - e.g. 0.033, 0.066 and 0.100 seconds, instead of the 6 time-delays - 0.0167, 0.0334, 0.0501, 0.0668, 0.0835, 0.1002 seconds used in your Plume Geometry study.

3. **Data submission:**
   Please submit data electronically for the lots of the test and reference products in spread-sheet format as attached herewith. Test/Reference ratios based on geometric means are also requested. Please note that the minimum ANDA batch size should be 5000 bottle. Please indicate the number of bottles in each lot of the test product.

Sincerely yours,

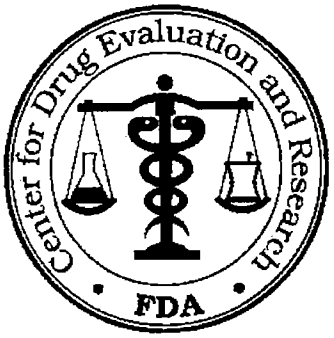
for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MAJOR AMENDMENT

ANDA 76-103

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUL - 3 2001



TO: APPLICANT: Bausch & Lomb Pharmaceuticals, Inc.

TEL: (813) 975-7700 Ext 7102

ATTN: Joseph Hawkins

FAX: (813) 975-7757

FROM: Michelle Dillahunt

PROJECT MANAGER: 301-827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated January 17, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ipratropium Bromide Nasal Spray, 0.06%.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (10 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance

SPECIAL INSTRUCTIONS: Chemistry and Labeling comments included.

7/3/01

Redacted 7 page(s)

of trade secret and/or

confidential commercial

information from

7/3/2001 FDA FAX

13. [redacted]

14. [redacted]

15. [redacted]

16. Bioequivalence for this product has not been established. Please respond to the deficiencies provided to you on May 30, 2001.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide any additional stability data that may be available.

2. We require an acceptable Methods Validation to support the ANDA and will schedule the study after the test method issues are resolved. Please provide a commitment to work with us to expeditiously resolve any deficiencies from the Methods Validation study if the ANDA is approved

prior to its completion. Additionally, please provide all current methods for drug substance acceptance and drug product release in a separate section of your amendment to facilitate the process.

3. Labeling deficiencies will also need to be addressed in your reply.

4. An acceptable compliance evaluation is necessary for approval. We have requested an evaluation from the Office of Compliance.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-103 Date of Submission: Jan. 17. 01
Applicant's Name: Bausch & Lomb
Established Name: Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) - 0.042 mg/spray)

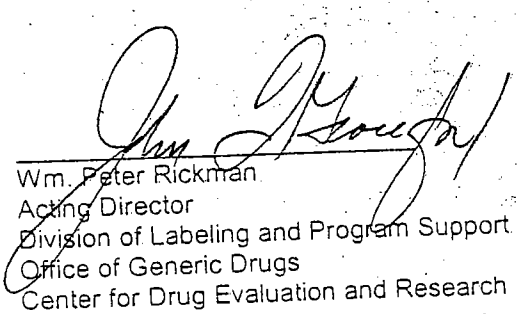
Labeling Deficiencies:

1. CONTAINER 42 mcg/spray (165 sprays) - Revise the product name to read: Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) rather than Ipratropium Bromide Nasal Spray 0.06%
2. CARTON – 42 mcg/spray (1 x165 sprays) – See revised name change
3. INSERT – See revised name change.
4. PATIENT LEAFLET – See revised name change.

Please revise your labels and labeling, as instructed above, and submit 12 final print labels and labeling or draft if you prefer.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BAUSCH & LOMB

8500 Hidden River Parkway
Tampa, Florida 33637

Facsimile Transmission Cover

NUMBER OF PAGES (Including cover): 8

DATE: September 26, 2001

BIOAVAILABILITY
N/A

TO: Krista Scardina Phone: 301-827-5847
Fax: 301-594-0181

From: Joe Hawkins Phone: 813-866-2102
Fax: 813-975-7757

Subject: ANDA August 10 Conference regarding ANDAs 76-025 & 76-103

Krista,

We participated in a conference call with the Agency on August 10, 2001 regarding the subject ANDAs. FDA requested that we provide data demonstrating the stage of plume development where droplet size is evaluated. Please evaluate the attached proposal for evaluating droplet size and let me know if it is acceptable to the Division of Bioequivalence.

FDA also indicated that they want us to submit the data obtained from additional studies in a format of a template to be provided by the Agency. We have not received the template and would like to obtain it in electronic format if possible.

To reply or if you have any questions regarding this fax you may contact me at 813-866-2102 or by e-mail at: joe_hawkins@bausch.com.

Redacted 7 page(s)

of trade secret and/or

confidential commercial

information from

9/26/2001 BAUSCH & LOMB FAX

ANDA 76-103

CERTIFIED MAIL-RETURN RECEIPT REQUESTED

Bausch & Lomb Pharmaceuticals, Inc.
Attention: Joseph B. Hawkins
8500 Hidden River Parkway
Tampa, FL 33637

MAR 28 2002

Dear Sir:

This letter is in reference to your Abbreviated New Drug Application (ANDA) dated January 17, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ipratropium Bromide Nasal Solution, 0.06%.

We refer you to our "Not Approvable" letter dated July 3, 2001, which detailed the deficiencies identified during our review of your ANDA. The Agency may consider an ANDA applicant's failure to respond to a "Not Approvable" letter within 180 days to be a request by the applicant to withdraw the ANDA under 314.120(b). Your amendment to the application is overdue. You must amend your application within 10 days of receipt of this letter. Otherwise, an action to withdraw the application will be initiated per 21 CFR 314.99.

If you do not wish to pursue approval of this application at this time, you should request withdrawal in accord with 21 CFR 314.65. A decision to withdraw the application would be without prejudice to refiling.

APPEARS THIS WAY
ON ORIGINAL

If you have further questions you may contact Saundra T. Middleton, Project Manager, Regulatory Support Branch, at (301) 827-5862.

Please send all correspondence to the following address:

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Sincerely yours,

S. Middleton for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA # 76-103
DUP/Division File
HFD-610/PRickman
Endorsement:
HFD-617/GDavis, Chief, RSB, S. Middleton for date 3/28/02
HFD-617SMiddleton, CSO, S. Middleton date 3/28/02
Word File
V:\FIRMSAM/BAUSCH/LTRS&REV/76103.OTH
F/T by EEH 03/28/02

10 DAY LETTER!

8500 Hidden River Parkway
Tampa FL 33637
www.bausch.com

BAUSCH & LOMB

April 11, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Label
ORIG AMENDMENT
Ac

Re: ANDA 76-103, Ipratropium Bromide Nasal Spray, 0.06%
Major Amendment – Chemistry Issues

Dear Sir or Madam:

This correspondence is submitted in response to the Agency's July 3, 2001, "not approvable" facsimile for the above referenced application. In that letter, the Agency indicated that our response would be considered a major amendment. A copy of the Agency's letter is provided in Attachment 1.

To facilitate the Agency's review, each of the questions and our corresponding response is included following the FDA form 365h. Necessary supporting documentation for each response is provided in attachments to this amendment.

We believe that this correspondence provides a thorough response to the questions raised in the Agency's July 3, 2001 correspondence. The information contained in this amendment is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

If you have any questions regarding this correspondence or need additional information, please contact Joe Hawkins by telephone at (813) 866-2102, or by fax at (813) 975-7757.

Sincerely,

J. B. Hawkins

Joseph B. Hawkins
Manager,
Regulatory Affairs

enclosure

RECEIVED
APR 12 2002
OGD / CDER

8500 Hidden River Parkway
Tampa FL 33637
Tel 813 975 7700
www.bausch.com

BAUSCH & LOMB

April 15, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AA

Re: ANDA 76-103, Ipratropium Bromide Nasal Spray, 0.06%
Current Drug Substance and Drug Product Methods

Dear Sir or Madam:

This correspondence is submitted to provide copies of current drug substance acceptance and drug product release methods in a separate section as requested in the Agency's July 3, 2001, "not approvable" facsimile for the above referenced application. This information is provided in addition to our April 11, 2002 response to deficiencies described in the Agency's facsimile.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

If you have any questions regarding this correspondence or need additional information, please contact Joe Hawkins by telephone at (813) 866-2102, or by fax at (813) 975-7757.

Sincerely,

JB Hawk

Joseph B. Hawkins
Manager,
Regulatory Affairs

enclosure

Noted
TC
5/3/02

RECEIVED
APR 17 2002
OGD / CDER

NDA 76-103

MINOR AMENDMENT

ANDA 76-103

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

AUG 13 2002

TO: APPLICANT: Bausch & Lomb Pharmaceuticals, Inc.
ATTN: Joseph B. Hawkins

TEL: 813-866-2102

FAX: 813-975-7757

FROM: Peter Chen

PROJECT MANAGER: 301-827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated January 17, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ipratropium Bromide Nasal Spray, 0.06%.

Reference is also made to your amendment(s) dated: April 11 and April 15, 2002.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS: Chemistry comments included.

TC 8/13/02

Redacted 2 page(s)

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information from

8/13/2002 FDA FAX

8500 Hidden River Parkway
Tampa FL 33637
www.bausch.com

BAUSCH & LOMB

August 29, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

[redacted]AMENDMENT
N/AM

Re: ANDA 76-103, Ipratropium Bromide Nasal Spray, 0.06%
Minor Amendment – Chemistry Issues

Dear Sir or Madam:

This correspondence is submitted in response to the Agency's August 13, 2002, "not approvable" facsimile for the above referenced application. In that communication, the Agency indicated that our response would be considered a Minor Amendment. A copy of the Agency's facsimile is enclosed in Attachment 1.

To facilitate the Agency's review, each of the questions and our corresponding response is included following the FDA form 365h. Necessary supporting documentation for each response is provided in attachments to this amendment.

We believe that this correspondence provides a thorough response to the questions raised in the Agency's August 13, 2002 facsimile. The information contained in this amendment is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

If you have any questions regarding this correspondence or need additional information, please contact Joe Hawkins by telephone at (813) 866-2102, or by fax at (813) 975-7757.

Sincerely,

J.B. Hawk -

Joseph B. Hawkins
Manager,
Regulatory Affairs

enclosure

RECEIVED
AUG 30 2002
OGD / CDER

MINOR AMENDMENT

SEP 18 2002

ANDA 76-103

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Bausch & Lomb Pharmaceuticals, Inc.
ATTN: Joseph B. Hawkins

TEL: 813-866-2102

FAX: 813-975-7757

FROM: Peter Chen

PROJECT MANAGER: 301-827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated January 17, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ipratropium Bromide Nasal Solution, 0.06%.

Reference is also made to your amendment(s) dated: August 29, 2002.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (1 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS: Chemistry Comments included.

PC 9/18/02

SEP 18 2002

38. Chemistry Comments to be Provided to the Applicant

ANDA: 76-103

APPLICANT: Bausch & Lomb Pharmaceuticals, Inc.

DRUG PRODUCT: Ipratropium Bromide Nasal Solution, 0.06%

The deficiencies presented below represent MINOR deficiencies.

1. Bioequivalence for the drug product has not been demonstrated. Please reply to this communication no earlier than your reply to the bioequivalence deficiencies dated May 30, 2001.

2. [redacted]

3. [redacted]

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

8500 Hidden River Parkway
Tampa FL 33637
www.bausch.com

BAUSCH & LOMB

September 19, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AB
BIOAVAILABILITY

Re: ANDA 76-103, Ipratropium Bromide Nasal Spray, 0.06%
Bioequivalence Amendment

Dear Sir or Madam:

This correspondence is submitted in response to the Agency's May 30, 2001, facsimile regarding bioequivalence issues for the above referenced application. In that letter, the Agency indicated that our response would be considered a major amendment. A copy of the Agency's letter is provided in Attachment 1.

To facilitate the Agency's review, a table of contents for the enclosed information is provided following the FDA form 365h. Necessary supporting documentation for each response is provided in attachments to this amendment. We believe that this correspondence provides a complete response to the questions raised in the Agency's May 30, 2001 correspondence.

The information contained in this amendment is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

If you have any questions regarding this correspondence or need additional information, please contact me by telephone at (813) 866-2102, or by fax at (813) 975-7757.

Sincerely,

J. B. Hawkins

Joseph B. Hawkins
Manager,
Regulatory Affairs

enclosure

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SEP 2 0 2002
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8500 Hidden River Parkway
Tampa FL 33637
Tel 813 975 7700
www.bausch.com

BAUSCH & LOMB

October 3, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT
N/am

Re: ANDA 76-103, Ipratropium Bromide Nasal Spray, 0.06%
Minor Amendment – Chemistry Issues

Dear Sir or Madam:

This correspondence is submitted in response to the Agency's September 18, 2002, "not approvable" facsimile for the above referenced application. In that communication, the Agency indicated that our response would be considered a Minor Amendment. A copy of the Agency's facsimile is enclosed in Attachment 1.

To facilitate the Agency's review, each of the questions and our corresponding response is included following the FDA form 365h. Necessary supporting documentation for each response is provided in attachments to this amendment.

We believe that this correspondence provides a thorough response to the questions raised in the Agency's September 18, 2002 facsimile. The information contained in this amendment is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

If you have any questions regarding this correspondence or need additional information, please contact Joe Hawkins by telephone at (813) 866-2102, or by fax at (813) 975-7757.

Sincerely,

Joseph B. Hawkins
Manager,
Regulatory Affairs

enclosure

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8500 Hidden River Parkway
Tampa FL 33637
www.bausch.com

BAUSCH & LOMB

March 20, 2003

NEW CORRESP
NC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: ANDA 76-103, Ipratropium Bromide Nasal Spray, 0.06%
Telephone Amendment – Method Validation Commitment

Dear Sir or Madam:

This correspondence is submitted in response to a March 19, 2003, from Sara Ho regarding the above referenced application. Sara requested that we provide certification that we would work with the Agency to resolve any method validation issues, should the application be approved prior to completion of the FDA method validation.

Bausch & Lomb commits to work with the Agency to expeditiously resolve any deficiencies from the Methods Validation study if the ANDA is approved prior to its completion.

If you have any questions regarding this correspondence, please contact me at the above address or by telephone at (813) 866-2102.

Sincerely,

Joseph B. Hawkins
Manager,
Regulatory Affairs

Enclosure

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NCA
TC 4/2/03

8500 Hidden River Parkway
Tampa FL 33637
www.bausch.com

BAUSCH
& LOMB

March 25, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRESP
NC

Re: ANDA 76-103, Ipratropium Bromide Nasal Spray, 0.06%
Telephone Amendment – Administrative Issues

Dear Sir or Madam:

This correspondence is submitted in response to the Agency's March 25, 2003, telephone request regarding the above referenced application. Specifically, Bob West called to request that we provide certification that we would not market our product for an indication protected by exclusivity until October 27, 2003. The requested certification is enclosed.

The information contained in this amendment is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

If you have any questions regarding this correspondence or need additional information, please contact Joe Hawkins by telephone at (813) 866-2102, or by fax at (813) 975-7757.

Sincerely,

J B. Hawk

Joseph B. Hawkins
Director, Regulatory Affairs

Enclosure

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MAR 26 2003
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